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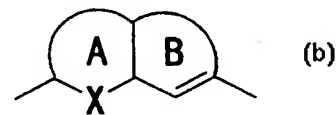
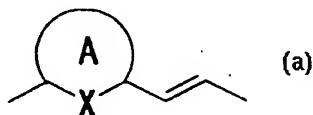
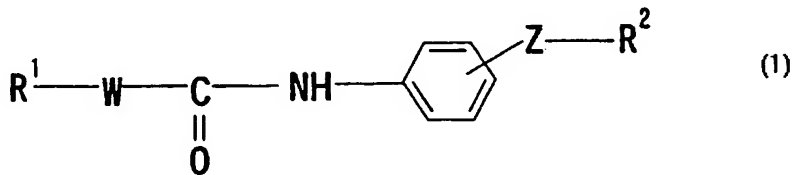
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(54) Title: PHARMACEUTICAL COMPOSITION FOR ANTAGONIZING CCR5 COMPRISING ANILIDE DERIVATIVE

(57) Abstract

This invention is to provide a pharmaceutical composition for antagonizing CCR5 which comprises a compound of formula (1) wherein R¹ is an optionally substituted 5- to 6-membered ring; W is a divalent group of formula (a) or (b) wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted C, N or O atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R² is an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, etc., or a salt thereof.



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DESCRIPTION

Pharmaceutical Composition for Antagonizing CCR5
comprising Anilide Derivative

5 Technical Field

The present invention relates to a pharmaceutical composition for antagonizing CCR5 comprising an anilide derivative.

10 Background Art

Recently, HIV (human immunodeficiency virus) protease inhibitors are developed for method of the treatment of AIDS (acquired immunological deficient syndrome) and use of the protease inhibitors in combination with conventional two
15 HIV reverse transcriptase inhibitors provides with a further progress of the treatment of AIDS. However, these drugs and their combination use are not sufficient for the eradication of AIDS, and development of new anti-AIDS drugs having different activity and mechanism are sought for.

20 As a receptor from which HIV invades to a target cell, CD4 is so far known, and recently CCR5 as a second receptor of macrophage-tropic HIV and CXCR4 as a second receptor of T cell-tropic HIV, each of which is G protein-coupled chemokine receptor having seven transmembrane domains, are
25 respectively found out. These chemokine receptors are thought to play an essential role in establishment and spread of HIV infection. In fact, it is reported that a person who is resistant to HIV infection in spite of several exposures retains mutation of homo deletion of CCR5 gene.
30 Therefore, a CCR5 antagonist is expected to be a new anti-HIV drug. However, so far, there has been no report that a CCR5 antagonist is developed as a therapeutic agent of AIDS.

In order to investigate an anti-AIDS drug having CCR5
35 antagonistic activity, it is necessary to clone CCR5 gene from human tissue derived cDNA library, to ligate said gene

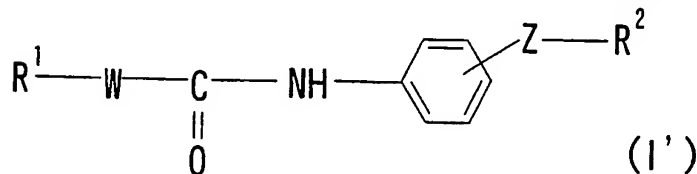
with a vector for expression in animal cells, to introduce said gene into animal cells and to obtain cells expressing CCR5. In addition, with using this transformant, it is necessary to screen a compound which strongly inhibits
5 binding of CC chemokine RANTES, natural ligand, to CCR5 (which strongly antagonizes CCR5). However, so far there has been no report on a low molecule compound having CCR5 antagonistic activity. The present invention is to provide a pharmaceutical composition which is useful for the
10 treatment or prophylaxis of infectious disease of HIV and, in particular, AIDS and which comprises an anilide derivative having CCR5 antagonistic activity.

Disclosure of Invention

15 The present inventors diligently made extensive studies on compounds having CCR5 antagonistic activity and, as a result, they found that an anilide derivative of the following formula (I') or a salt thereof [hereinafter, referred to as Compound (I')] unexpectedly possesses potent
20 CCR5 antagonistic activity and clinically desirable pharmaceutical effect (e.g. remarkable inhibition of HIV infection to human peripheral mononuclear cells, etc.).

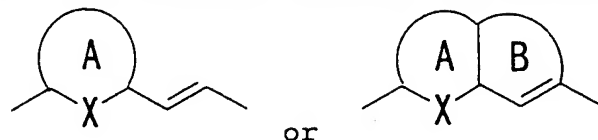
Based on the finding, the present invention was accomplished.

25 More specifically, the present invention relates to (1) a pharmaceutical composition for antagonizing CCR5 (or a pharmaceutical composition for inhibiting binding of a ligand to CCR5 or a pharmaceutical composition for antagonizing binding of a ligand of CCR5 to CCR5)
30 which comprises a compound of the formula (I'):

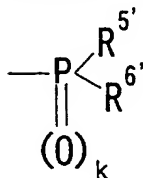


wherein R¹ is an optionally substituted 5- to 6-membered ring,

W is a divalent group of the formula:



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, the ring B is an optionally substituted 5- to 7-membered ring, Z is a chemical bond or a divalent group, R² is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^{5'} and R^{6'} are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R^{5'} and R^{6'} may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof;

(2) a composition of the above (1), wherein R¹ is benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted;

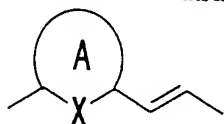
(3) a composition of the above (1), wherein R¹ is an optionally substituted benzene;

(4) a composition of the above (1), wherein the ring A is

furan, thiophene, pyrrole, pyridine or benzene, each of which may be substituted;

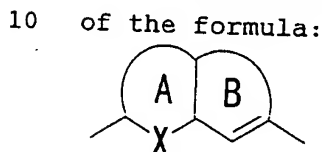
(5) a composition of the above (1), wherein the ring A is an optionally substituted benzene;

5 (6) a composition of the above (1), wherein W is a group of the formula:



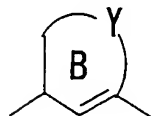
wherein each symbol is as defined in the above (1);

(7) a composition of the above (1), wherein W is a group of the formula:



wherein each symbol is as defined in the above (1);

(8) a composition of the above (7), wherein the ring B is a 5- to 7-membered ring group of the formula:



15

wherein Y is -Y'-(CH₂)_n- (Y' is -S-, -O-, -NH- or -CH₂-, and n is an integer of 0-2), -CH=CH- or -N=CH-), which may have a substituent at any possible position;

(9) a composition of the above (8), wherein Y is -Y'-(CH₂)₂- (Y' is -S-, -O-, -NH- or -CH₂-);

20 (10) a composition of the above (8), wherein Y is -(CH₂)₂-, -(CH₂)₃- or -O-(CH₂)₂-;

(11) a composition of the above (10), wherein the ring A is an optionally substituted benzene;

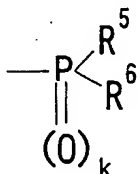
25 (12) a composition of the above (1), wherein Z is an optionally substituted C₁₋₃ alkylene;

(13) a composition of the above (1), wherein Z is a divalent group of the formula: -Z'-(CH₂)_n- (Z' is -CH(OH)-, -C(O)- or -CH₂-, and n is an integer of 0-2) in which an optional

30 methylene group may be substituted;

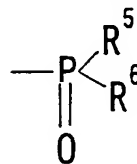
(14) a composition of the above (1), wherein Z is methylene;
 (15) a composition of the above (1), wherein Z is substituted
 at para position of the benzene ring;

- (16) a composition of the above (1), wherein R² is (1) an
 5 optionally substituted amino group in which a nitrogen atom
 may form a quaternary ammonium, (2) an optionally
 substituted nitrogen-containing heterocyclic ring group
 which may contain a sulfur atom or an oxygen atom as ring
 constituting atoms and wherein a nitrogen atom may form a
 10 quaternary ammonium, (3) a group binding through a sulfur
 atom or (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may
 form a phosphonium; and R⁵ and R⁶ are independently an
 15 optionally substituted hydrocarbon group or an optionally
 substituted amino group, and R⁵ and R⁶ may bind to each other
 to form a cyclic group together with the adjacent phosphorus
 atom;

- (17) a composition of the above (1), wherein R² is (1) an
 20 optionally substituted amino group in which a nitrogen atom
 may form a quaternary ammonium, (2) an optionally
 substituted nitrogen-containing heterocyclic ring group
 which may contain a sulfur atom or an oxygen atom as ring
 constituting atoms and wherein a nitrogen atom may form a
 25 quaternary ammonium or (3) a group of the formula:



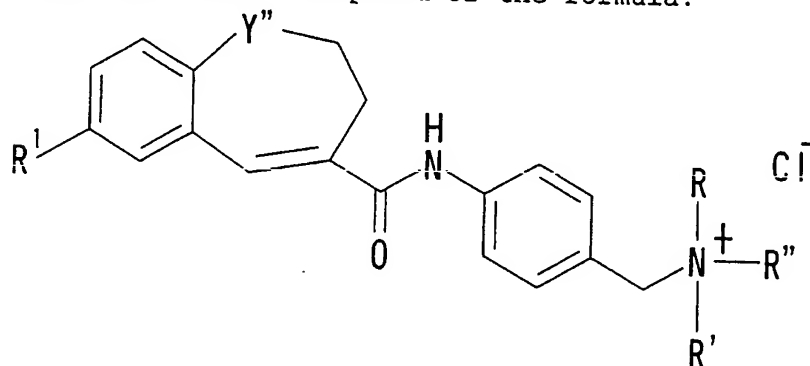
- wherein R⁵ and R⁶ are independently an optionally substituted
 hydrocarbon group, and R⁵ and R⁶ may bind to each other to
 form a cyclic group together with the adjacent phosphorus
 30 atom;

(18) a composition of the above (1), wherein R' is an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium;

(19) a composition of the above (1), wherein R' is a group of the formula: -N⁺RR'R"

wherein R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(20) a pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



wherein R¹ is an optionally substituted benzene or an optionally substituted thiophene; Y'' is -CH₂-, -S- or -O-; and R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(21) a composition of the above (20), wherein R and R' are independently an optionally substituted acyclic hydrocarbon group;

(22) a composition of the above (20), wherein R and R' are independently an optionally substituted C₁₋₆ alkyl group;

(23) a composition of the above (20), wherein R'' is an optionally substituted alicyclic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(24) a composition of the above (20), wherein R'' is an optionally substituted C₃₋₆ cycloalkyl group;

(25) a composition of the above (20), wherein R'' is an

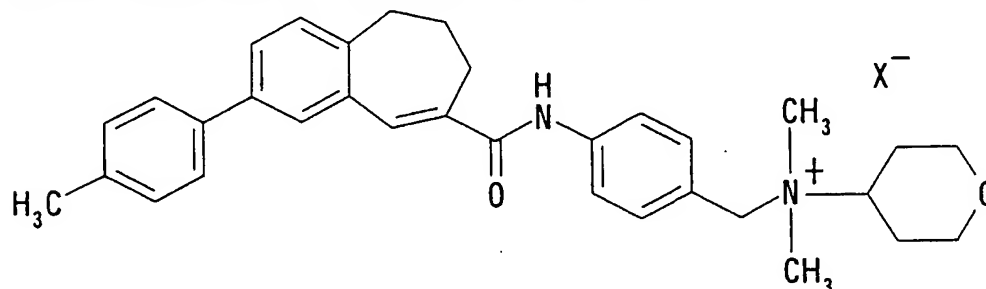
optionally substituted cyclohexyl;

(26) a composition of the above (20), wherein R" is an optionally substituted saturated alicyclic heterocyclic ring group;

5 (27) a composition of the above (20), wherein R" is an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl;

(28) a composition of the above (20), wherein R" is an optionally substituted tetrahydropyranyl;

10 (29) a pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



wherein X⁻ is an anion.

15 (30) a composition of the above (29), wherein X is a halogen atom;

(31) a pharmaceutical composition for antagonizing CCR5 which comprises

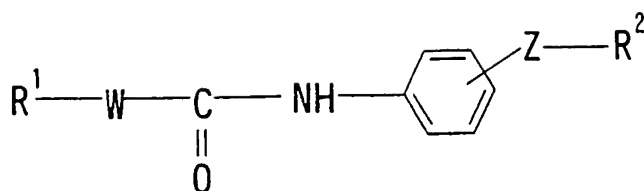
20 N-methyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-piperidinium iodide,

N-methyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]piperidinium iodide,

25 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboximide,

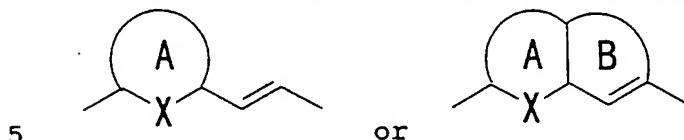
30 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepine-4-carboximide,

- 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide,
- N,N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium iodide,
- 5 N,N-dimethyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(4-oxocyclohexyl)ammonium chloride,
- 10 N,N-dimethyl-N-[4-[[[7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium chloride,
- or a salt thereof;
- (32) a composition of the above (1), which is for the
- 15 treatment or prophylaxis of infectious disease of HIV;
- (33) a composition of the above (1), which is for the treatment or prophylaxis of AIDS;
- (34) a composition of the above (1), which is for the prevention of the progression of AIDS;
- 20 (35) a composition of the above (32), which is used in combination with a protease inhibitor and/or a reverse transcriptase inhibitor;
- (36) a composition of the above (35), wherein the reverse transcriptase inhibitor is zidovudine, didanosine,
- 25 zalcitabine, lamivudine, stavudine, nevirapine or delavirdine;
- (37) a composition of the above (35), wherein the protease inhibitor is saquinavir, ritonavir, indinavir or nelfinavir;
- 30 (38) use of the compound of the above (1) or a salt thereof in combination with a protease inhibitor and/or a reverse transcriptase inhibitor for the treatment or prophylaxis of infectious disease of HIV;
- (39) a method for antagonizing CCR5 which comprises
- 35 administering to a mammal in need thereof an effective amount of a compound of the formula:

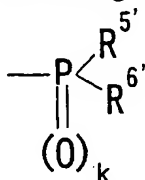


wherein R^1 is an optionally substituted 5- to 6-membered ring;

W is a divalent group of the formula:

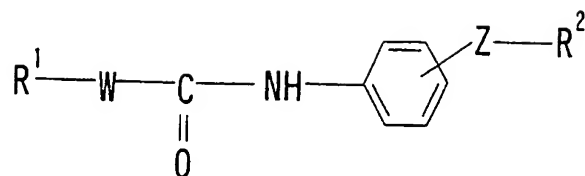


wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



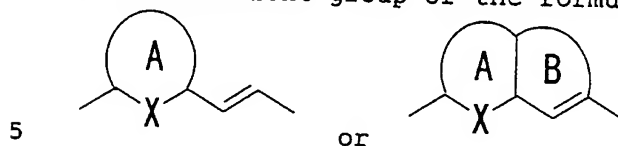
wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof;

(40) use of a compound of the formula:

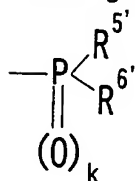


wherein R^1 is an optionally substituted 5- to 6-membered ring;

W is a divalent group of the formula:



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof, for the manufacture of a medicament for antagonizing CCR5; etc.

In the above formula (I'), examples of the "5- to

6-membered ring" of the "optionally substituted 5- to 6-membered ring" represented by R^1 include a 6-membered aromatic hydrocarbon such as benzene, etc.; a 5- to 6-membered aliphatic hydrocarbon such as cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, etc.; 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; etc. Among others, benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran (preferably, 6-membered ring), etc. are preferable, and in particular, benzene is preferable.

Example of the "substituents" which the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 may have include halogen atom, nitro, cyano, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted hydroxy group, an optionally substituted thiol group wherein a sulfur atom may be optionally oxidized to form a sulfinyl group or a sulfonyl group, an optionally substituted amino group, an optionally substituted acyl, an optionally esterified carboxyl group, an optionally substituted aromatic group,

etc.

Examples of the halogen as the substituents for R¹ include fluorine, chlorine, bromine, iodine, etc. Among others, fluorine and chlorine are preferable.

5 Examples of the alkyl in the optionally substituted alkyl as the substituents for R¹ include a straight or branched C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., and
10 preferably lower (C₁₋₆) alkyl.

 Examples of the substituents in the optionally substituted alkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally
15 halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

20 Examples of the cycloalkyl in the optionally substituted cycloalkyl as the substituents for R¹ include C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

 Examples of the substituents in the optionally substituted cycloalkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an
25 optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄
30 alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

35 Examples of the substituents in the optionally substituted hydroxy group as the substituents for R¹ include

- (1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C₃₋₇ cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted aralkyl (e.g. phenyl-C₁₋₄ alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (6) an optionally substituted acyl (e.g. C₂₋₄ alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and (7) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the

number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted thiol group as the substituents for R¹ are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for R¹, and among others,

- (1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted aralkyl (e.g. phenyl-C₁₋₄ alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (4) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted amino group as the substituents for R¹ are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for R¹, and examples of the optionally substituted amino group as the

- substituents for R¹ include an amino group which may have one to two substituents selected from the above-described substituents in the optionally substituted hydroxy group as the substituents for R¹, etc. Among others, as the
- 5 substituents in the optionally substituted amino group as the substituents for R¹,
- (1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl,
- 10 heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- 15 (3) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C₃₋₇ cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl,
- 20 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted acyl (e.g. C₂₋₁₀ alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- 25 (6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents, which each of the above-described (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally

30 substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group,

35 an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy

(e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The substituents in the optionally substituted amino group as the substituents for R¹ may bind to each other to form a cyclic amino group (e.g. 5- to 6-membered cyclic amino, etc. such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.). Said cyclic amino group may have a substituent, and examples of the substituents include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally substituted acyl as the substituents for R¹ include a carbonyl group or a sulfonyl group binding to

- (1) hydrogen;
- (2) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (3) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (4) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (5) an optionally substituted cycloalkenyl (e.g. C₃₋₇

cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(6) an optionally substituted 5- to 6-membered monocyclic aromatic group (e.g. phenyl, pyridyl, etc.); etc.

5 Examples of the acyl include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl, methanesulfonyl, ethanesulfonyl, etc.

10 Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted 5- to 6-membered monocyclic aromatic group may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

25 Examples of the optionally esterified carboxyl group as the substituents for R¹ include a carbonyloxy group binding to

(1) hydrogen;

30 (2) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);

35 (3) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

- (4) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (5) an optionally substituted cycloalkenyl (e.g. C₃₋₇ cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc., and preferably carboxyl, lower (C₁₋₆) alkoxycarbonyl, aryloxy carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, naphthoxycarbonyl, etc.), etc.

Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the aromatic group in the optionally substituted aromatic group as the substituents for R¹ include 5- to 6-membered homocyclic or heterocyclic ring aromatic ring, etc. such as phenyl, pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, etc.

Examples of the substituents for these aromatic group include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g.

trifluoromethyl, methyl, ethyl, etc.), an optionally
halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy,
trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g.
acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g.
5 methanesulfonyl, ethanesulfonyl, etc.), etc., and the
number of the substituents are preferably 1 to 3.

The number of the above-mentioned substituents for R¹
is 1-4 (preferably 1-2) and they may be same or different
and present at any possible position on the ring represented
10 by R¹. When two or more substituents are present on the 5-
to 6-membered ring in the "an optionally substituted 5- to
6-membered ring" represented by R¹, two substituents among
them may bind to each other to form a lower (C₁₋₆) alkylene
(e.g. trimethylene, tetramethylene, etc.), a lower (C₁₋₆)
15 alkyleneoxy (e.g. -CH₂-O-CH₂-, -O-CH₂-CH₂-, etc.), a lower
(C₁₋₆) alkylenedioxy (e.g. -O-CH₂-O-, -O-CH₂-CH₂-O-, etc.),
a lower (C₁₋₆) alkenylene (e.g. -CH₂-CH=CH-, -CH₂-CH₂-CH=CH-,
-CH₂-CH=CH-CH₂-, etc.), a lower (C₄₋₆) alkadienylene (e.g.
-CH=CH-CH=CH-, etc.), etc.

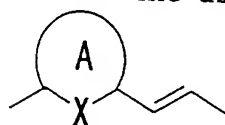
20 Preferred examples of the "substituents", which the
"5- to 6-membered ring" in the "an optionally substituted
5- to 6-membered ring" represented by R¹ may have, include
an optionally halogenated lower (C₁₋₄) alkyl (e.g. methyl,
ethyl, t-butyl, trifluoromethyl, etc.), an optionally
25 halogenated lower (C₁₋₄) alkoxy (e.g. methoxy, ethoxy, t-
butoxy, trifluoromethoxy, etc.), halogen (e.g. fluorine,
chlorine, etc.), nitro, cyano, an amino group optionally
substituted with 1-2 lower (C₁₋₄) alkyl groups (e.g. amino,
methylamino, dimethylamino, etc.), 5- to 6-membered cyclic
30 amino (e.g. 1-pyrrolidinyl, 1-piperazinyl, 1-piperidinyl,
4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-
tetrahydropyranyl, etc.), etc., and when R¹ is a benzene,
the "substituent" is preferably present at para position.

In the above formula (I'), examples of the "5- to
35 6-membered aromatic ring" in the "optionally substituted
5- to 6-membered aromatic ring" represented by A include

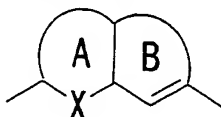
6-membered aromatic hydrocarbon such as benzene, etc.; 5-
to 6-membered aromatic heterocyclic ring containing 1 to
3 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms
selected from oxygen atom, sulfur atom and nitrogen atom
such as furan, thiophene, pyrrole, imidazole, pyrazole,
thiazole, oxazole, isothiazole, isoxazole, pyridine,
pyrazine, pyrimidine, pyridazine, triazole, etc.; etc.
Among others, benzene, furan, thiophene, pyridine
(preferably, 6-membered ring) etc. are preferable, and in
particular benzene is preferable.

Examples of the "substituents", which the "5- to
6-membered aromatic ring" in the "optionally substituted
5- to 6-membered aromatic ring" represented by A may have,
are similar to the "substituents" which the "5- to 6-membered
ring" in the "optionally substituted 5- to 6-membered ring"
represented by R¹ may have. The number of said substituents
for the ring A is 1-4 (preferably 1-2), and they may be same
or different and present at any possible position (e.g. the
position of the group X and the other positions) on the ring
represented by A.

In the above formula (I'), a group of the formula:

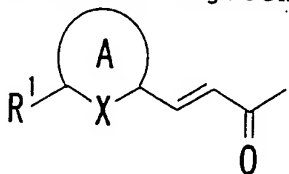


or

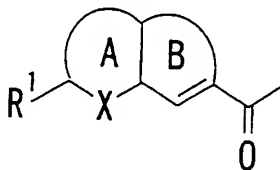


represented by W

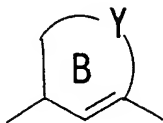
binds to adjacent groups in the following manner:



or



In the above formula (I'), examples of the "5- to
7-membered ring" in the "optionally substituted 5- to
7-membered ring" represented by B include a 5- to 7-membered
ring group of the formula:



, which may have a substituent at any possible position, etc.

- In the above formula, the divalent group represented by Y may be any divalent group as far as the ring B forms an optionally substituted 5- to 7-membered ring, and preferred examples of the divalent groups include
- (1) $-(CH_2)_{a_1}-O-(CH_2)_{a_2}-$ (a_1 and a_2 are same or different and 0, 1 or 2, provided that the sum of a_1 and a_2 is 2 or less), $-O-(CH=CH)-$, $-(CH=CH)-O-$;
 - (2) $-(CH_2)_{b_1}-S-(CH_2)_{b_2}-$ (b_1 and b_2 are same or different and 0, 1 or 2, provided that the sum of b_1 and b_2 is 2 or less), $-S-(CH=CH)-$, $-(CH=CH)-S-$;
 - (3) $-(CH_2)_{d_1}-$ (d_1 is 1, 2 or 3), $-CH_2-(CH=CH)-$, $-(CH=CH)-CH_2-$, $-CH=CH-$;
 - (4) $-(CH_2)_{e_1}-NH-(CH_2)_{e_2}-$ (e_1 and e_2 are same or different and 0, 1 or 2, provided that the sum of e_1 and e_2 is 2 or less), $-NH-(CH=CH)-$, $-(CH=CH)-NH-$, $-(CH_2)_{e_6}-(N=CH)-(CH_2)_{e_7}-$, $-(CH_2)_{e_7}-(CH=N)-(CH_2)_{e_6}-$ (one of e_6 and e_7 is 0, and the other is 1), $-(CH_2)_{e_8}-(N=N)-(CH_2)_{e_9}-$ (one of e_8 and e_9 is 0, and the other is 1); etc. More preferred examples of the divalent groups include $-O-$, $-O-CH_2-$, $-O-CH_2-CH_2-$, $-O-CH=CH-$, $-S-$, $-S-CH_2-$, $-S-CH_2-CH_2-$, $-S-CH=CH-$, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-NH-$, $-N=CH-$, $-CH=N-$, $-N=N-$ (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc.

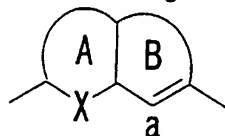
The divalent group may have a substituent. Examples of the substituent include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 and an oxo group, etc. Among others, a lower (C_{1-3}) alkyl (e.g. methyl, ethyl, propyl, etc.), a phenyl group, an oxo group, a hydroxy group, etc. are preferable. In addition, the divalent group may be $-O-C(O)-$ (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc.

The number of the substituents are preferably 1 to 4 (preferably, 1-2), and they may be same or different and bind to the divalent group at any possible position.

As the divalent group represented by Y, a group of the formula: $-Y'-(CH_2)_m-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), $-CH=CH-$, $-N=CH-$, $-(CH_2)_m-Y'$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), $-CH=N-$ (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc. is preferable. Among others, a group of the formula: $-Y'-(CH_2)_m-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), $-CH=CH-$, $-N=CH-$ (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc. is preferable. In particular, Y is preferably a group of the formula: $-Y'-(CH_2)_2-$ (Y' is -S-, -O-, -NH- or $-CH_2-$ (preferably -S-, -O- or $-CH_2-$, more preferably -O- or $-CH_2-$)) in which the formula binds to the ring A through its left chemical bond, etc.; and the ring B is preferably a 7-membered ring. As the divalent group represented by Y, a group of the formula: $-(CH_2)_2-$, $-(CH_2)_3-$ or $-O-(CH_2)_2-$ is preferable.

Examples of the "substituents", which the "5- to 7-membered ring" in the "optionally substituted 5- to 7-membered ring" represented by B may have, include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R' and an oxo group, etc. The number of the substituents are preferably 1 to 4 (preferably, 1-2), and they may be same or different and bind to the divalent group at any possible position.

In a group of the formula:



represented by W, a carbon atom at the position a is preferably unsubstituted.

In the above formula (I'), examples of the divalent group represented by Z include an optionally substituted divalent group whose straight chain is constituted by 1 to 4 carbon atoms (e.g. C₁₋₄ alkylene, C₂₋₄ alkenylene, etc., preferably C₁₋₃ alkylene, more preferably methylene), etc.

The group Z may be bound to any possible position of the benzene ring, and preferably to para position of the benzene ring.

The divalent group represented by Z may be any divalent group whose straight chain is constituted by 1 to 4 atoms and exemplified by an alkylene chain of the formula: $-(CH_2)_{k_1}-$ (k_1 is an integer of 1-4), an alkenylene chain of the formula: $-(CH_2)_{k_2}-(CH=CH)-(CH_2)_{k_3}-$ (k_2 and k_3 are same or different and 0, 1 or 2, provided that the sum of k_2 and k_3 is 2 or less), etc.

Examples of the substituent for the divalent group represented by Z include any one which is capable of binding to the straight chain of the divalent group, and preferably C₁₋₆ lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.), lower (C₃₋₇) cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), an optionally esterified phosphono group, an optionally esterified carboxyl group, hydroxy group, oxo, etc., and more preferably C₁₋₆ lower alkyl (preferably C₁₋₃ alkyl), hydroxy group, oxo, etc.

Examples of the optionally esterified phosphono group include a group of the formula: $P(O)(OR')(OR'')$ wherein R' and R'' are independently hydrogen, a C₁₋₆ alkyl group or a C₃₋₇ cycloalkyl group, and R' and R'' may bind to each other to form a 5- to 7-membered ring.

In the above formula, examples of the C₁₋₆ alkyl group represented by R' and R'' include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc., and examples of the C₃₋₇ cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, cycloheptyl, etc. Among other, a straight C_{1-6} lower alkyl is preferable and C_{1-3} lower alkyl is more preferable. The groups R' and R'' may be same or different, and preferably the groups R' and R'' are same. When R' and R'' may bind to each other to form a 5- to 7-membered ring, the groups R' and R'' bind to each other to represent a straight C_{1-6} alkylene chain of the formula: $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, etc. Said chain may have a substituent, and examples of the substituent include hydroxy group, halogen, etc.

Examples of the optionally esterified carboxyl group include a carboxyl group and an ester group formed by binding a carboxyl group to a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.).

As the divalent group represented by Z, an optionally substituted C_{1-6} alkylene is preferable, and C_{1-3} alkylene which may be substituted by C_{1-3} alkyl, hydroxy group or oxo is more preferable.

Among others, as the divalent group represented by Z, a group of the formula: $-Z'-(CH_2)_n-$ or $-(CH_2)_n-Z'-$ (Z' is $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, and n is an integer of 0-2) in which each of the above formulas represent that it binds to the benzene ring through its left chemical bond and each of the methylene groups may be substituted by 1-2 same or different substituents is preferable, a group of the formula: $-Z'-(CH_2)_n-$ (Z' is $-CH(OH)-$, $-C(O)-$ or $-CH_2-$, and n is an integer of 0-2 (preferably, n is 0)) in which the formula binds to the benzene ring through its left chemical bond and each of the methylene groups may be substituted by 1-2 same or different substituents is more preferable, and methylene is particularly preferable.

In the above-mentioned formula (I'), examples of the "amino group" in the "optionally substituted amino group" in which a nitrogen atom may form a quaternary ammonium"

represented by R^2 include an amino group which may have 1-2 substituents, an amino group having 3 substituents wherein the nitrogen atom forms a quaternary ammonium, etc. When the number of the substituents on the nitrogen atom is 2 or more, these substituents may be same or different. When the total number of the substituents and hydrogen atoms on the nitrogen atom is 3, the "amino group" represented by R^2 may be any type of an amino group represented by the formula: $-N^+R_3$, $-N^+R_2R'$ or $-N^+RR'R''$ (R , R' and R'' are independently a hydrogen atom or a substituent). Examples of the counter anion of the amino group wherein the nitrogen atom forms a quaternary ammonium include an anion of a halogen atom (e.g. Cl^- , Br^- , I^- , etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others, Cl^- , Br^- , I^- , etc. are preferable.

Examples of the substituents for said amino group include

- (1) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C_{3-8} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.), provided that

- (2-1) said cycloalkyl may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrogen atom to

- form oxirane, thiorane, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran 1-oxide, piperidine, etc. (preferably, 6-membered ring such as tetrahydropyran, tetrahydrothiopyran, piperidine, etc.) and these groups preferably bind to the amino group at their 3- or 4-position (preferably, 4-position), that (2-2) said cycloalkyl may be fused with a benzene ring to form indane, tetrahydronaphthalene, etc. (preferably, indane, etc.), and that (2-3) said cycloalkyl may have a bridging comprising a straight chain constituted by 1-2 carbon atoms to form a bridged hydrocarbon residue such as bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, etc., preferably, a cyclohexyl group, etc. having a bridging comprising a straight chain constituted by 1-2 carbon atoms, and more preferably bicyclo[2.2.1]heptyl, etc.;
- (3) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{4-6}) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted aralkyl (e.g. phenyl- C_{1-4} alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (6) an optionally substituted acyl (e.g. C_{2-4} alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.);
- (8) an optionally substituted heterocyclic ring group (e.g. 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen

atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring
5 containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline,
10 piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, etc.; etc.; preferably 5- to 6-membered non-aromatic heterocyclic ring, etc.; more preferably 5- to 6-membered non-aromatic heterocyclic ring containing one
15 hetero-atom, etc. such as tetrahydrofuran, piperidine, tetrahydropyran, tetrahydrothiopyran, etc.); etc.

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl,
20 (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl, (7) optionally substituted aryl and (8) optionally substituted heterocyclic ring group may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally
25 halogenated lower (C_{1-4}) alkyl, an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{1-4} alkylenedioxy (e.g. $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, etc.), C_{1-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), phenyl-lower (C_{1-4}) alkyl, C_{1-4}
30 cycloalkyl, cyano, nitro, hydroxy group, thiol group, amino group, carboxyl group, lower (C_{1-4}) alkoxy-carbonyl (preferably, halogen, an optionally halogenated lower (C_{1-4}) alkyl, an optionally halogenated lower (C_{1-4}) alkoxy,
35 phenyl-lower (C_{1-4}) alkyl, C_{1-4} cycloalkyl, cyano, hydroxy group, etc.), etc., and the number of the substituents are

preferably 1 to 3.

- In the above formula (I'), preferred examples of the "optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium" represented by R' include
- 5 an amino group which may have 1-3 substituents selected from (1) a straight or branched lower (C₁₋₆) alkyl which may have 1 to 3 substituents selected from halogen, cyano, hydroxy group or C₃₋₇ cycloalkyl;
 - 10 (2) a C₃₋₈cycloalkyl which may have 1 to 3 substituents selected from halogen, an optionally halogenated lower (C₁₋₄) alkyl or phenyl-lower (C₁₋₄) alkyl, which may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrogen atom, which may be fused with a benzene ring, and which may have a bridging comprising a straight chain
 - 15 constituted by 1-2 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, tetrahydrothiapyranyl, piperidiny, indanyl, tetrahydronaphthalenyl, bicyclo[2.2.1]heptyl, etc., each of which may be substituted);
 - 20 (3) a phenyl-lower (C₁₋₄) alkyl which may have 1 to 3 substituents selected from halogen, an optionally halogenated lower (C₁₋₄) alkyl or an optionally halogenated lower (C₁₋₄) alkoxy;
 - (4) a phenyl which may have 1 to 3 substituents selected
 - 25 from halogen, an optionally halogenated lower (C₁₋₄) alkyl or an optionally halogenated lower (C₁₋₄) alkoxy; and
 - (5) a 5- to 6-membered aromatic heterocyclic ring (e.g. furan, thiophene, pyrrole, pyridine, etc.) which may have 1 to 3 substituents selected from halogen, an optionally
 - 30 halogenated lower (C₁₋₄) alkyl, an optionally halogenated lower (C₁₋₄) alkoxy, an optionally halogenated lower (C₁₋₄) alkoxy-lower (C₁₋₄) alkoxy, phenyl-lower (C₁₋₄) alkyl, cyano or hydroxy group.

In the above formula (I'), examples of the "nitrogen-containing heterocyclic ring" in the "optionally substituted nitrogen-containing heterocyclic ring group

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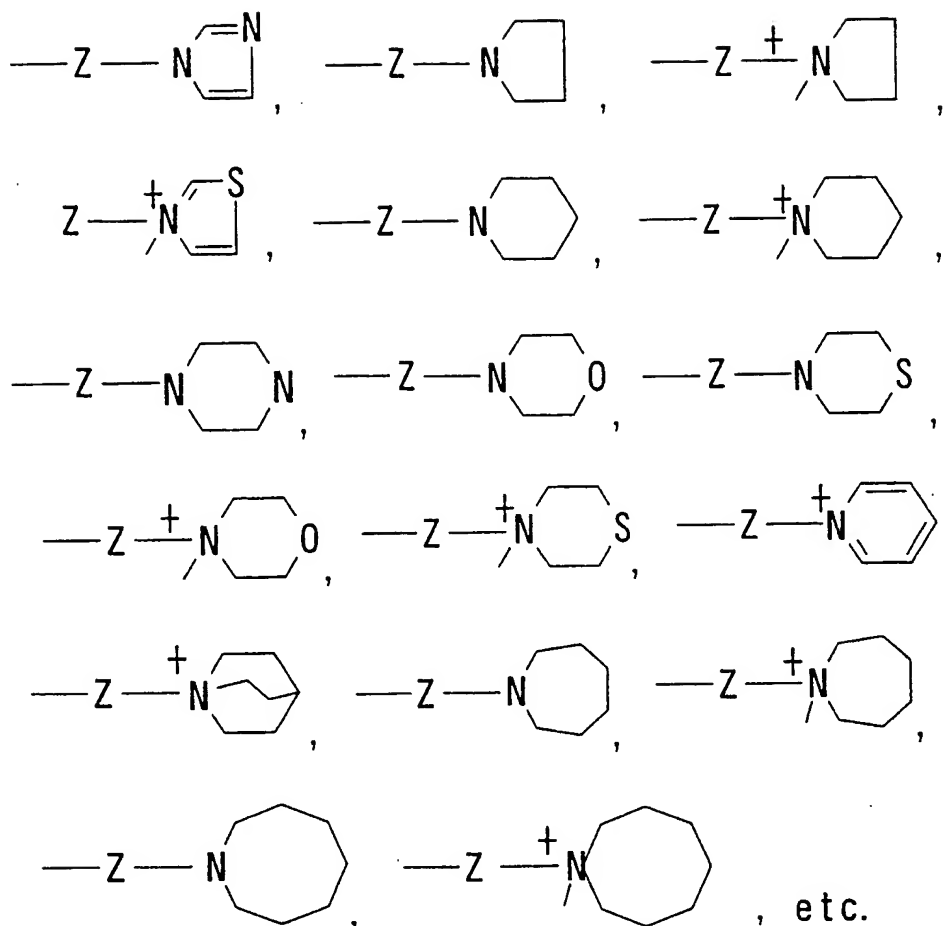
which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium" include a 5- to 6-membered aromatic heterocyclic ring which may contain 1 to 3 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom other than one nitrogen atom such as pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5-8 membered non-aromatic heterocyclic ring which may contain 1 to 3 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom other than one nitrogen atom such as pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, azacycloheptane, azacyclooctane (azocane), etc.; etc. These nitrogen-containing heterocyclic rings may have a bridging comprising a straight chain constituted by 1-2 carbon atoms to form a bridged nitrogen-containing heterocyclic ring azabicyclo[2.2.1]heptane, azabicyclo[2.2.2]octane (quinuclidine), etc. (preferably, piperidine having a bridging comprising a straight chain constituted by 1-2 carbon atoms, etc.).

Among the above-exemplified nitrogen-containing heterocyclic rings, pyridine, imidazole, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, azabicyclo[2.2.2]octane (preferably, a 6-membered ring) are preferable.

The nitrogen atom of said "nitrogen-containing heterocyclic ring" may form a quaternary ammonium or may be oxidized. When the nitrogen atom of said "nitrogen-containing heterocyclic ring" forms a quaternary ammonium, examples of the counter anion of the "nitrogen-containing heterocyclic ring wherein the nitrogen atom forms a quaternary ammonium" include an anion of a halogen atom (e.g.

Cl⁻, Br⁻, I⁻, etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others, Cl⁻, Br⁻, I⁻, etc. are preferable.

Said "nitrogen-containing heterocyclic ring" may bind to the divalent group represented by Z through either a carbon atom or a nitrogen atom, and may be 2-pyridyl, 3-pyridyl, 2-piperidinyl, etc. which binds to the divalent group represented by Z through a carbon atoms. Preferably, the "nitrogen-containing heterocyclic ring" binds to the divalent group represented by Z through a nitrogen atom, as exemplified by the following formulas:



Examples of the substituents, which said "nitrogen containing heterocyclic ring" may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally substituted lower (C_{1-4}) alkyl, an optionally substituted lower (C_{1-4}) alkoxy, an optionally substituted phenyl, an optionally substituted mono- or di-phenyl-lower (C_{1-4}) alkyl, an optionally substituted C_{1-4} cycloalkyl, cyano, nitro, hydroxy group, thiol group, amino group, carboxyl group, lower (C_{1-4}) alkoxy-carbonyl, lower (C_{1-4}) alkanoyl, lower (C_{1-4}) alkylsulfonyl, an optionally substituted heterocyclic ring group (e.g. 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom such as furan, thiophene, pyrrole,

imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; etc.), etc., and the number of the substituents is preferably 1-3.

Examples of the substituent, which the "optionally substituted lower (C_{1-4}) alkyl", the "optionally substituted lower (C_{1-4}) alkoxy", the "optionally substituted phenyl", the "optionally substituted mono- or di-phenyl-lower (C_{1-4}) alkyl", the "optionally substituted C_{3-7} cycloalkyl" and the "optionally substituted heterocyclic ring group" as a substituent for said "nitrogen-containing heterocyclic ring" may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally halogenated lower (C_{1-4}) alkyl, an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{1-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), cyano, nitro, hydroxy group, thiol group, amino group, carboxyl group, lower (C_{1-4}) alkoxy-carbonyl, etc., and the number of the substituents are preferably 1 to 3.

In the above formula (I'), preferred example of the substituents for the "nitrogen-containing heterocyclic ring" in the "optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium" include

(1) halogen, (2) cyano, (3) hydroxy group, (4) carboxyl group, (5) lower (C₁₋₄) alkoxy-carbonyl, (6) lower (C₁₋₄) alkyl which may be substituted with halogen, hydroxy group or lower (C₁₋₄) alkoxy, (7) lower (C₁₋₄) alkoxy which may be substituted with
5 halogen, hydroxy group or lower (C₁₋₄) alkoxy, (8) phenyl which may be substituted with halogen, lower (C₁₋₄) alkyl, hydroxy group, lower (C₁₋₄) alkoxy or C₁₋₃ alkylenedioxy, (9) mono- or di-phenyl-lower (C₁₋₄) alkyl whose benzene ring may be substituted with halogen, lower (C₁₋₄) alkyl, hydroxy group,
10 lower (C₁₋₄) alkoxy or C₁₋₃ alkylenedioxy, (10) 5- to 6-membered aromatic heterocyclic ring such as furan, thiophene, pyrrole, pyridine, etc., etc.

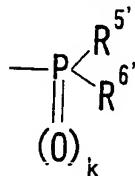
In the above formula (I'), examples of the "group binding through a sulfur atom" represented by R² include a
15 group of the formula: -S(O)_m-R^s wherein m is an integer of 0-2, and R^s is a substituent.

In the above formula, preferred examples of the "substituent" represented by R^s include
(1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such
20 as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
(2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
25 (3) an optionally substituted aralkyl (e.g. phenyl-C₁₋₄ alkyl (e.g. benzyl, phenethyl, etc.), etc.);
(4) an optionally substituted aryl (e.g. phenyl, naphthyl,
30 etc.) etc.

Examples of the substituent, which the above-mentioned
(1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) an optionally substituted aryl may have, include
35 halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group,

carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

In the above formula (I'), examples of the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^{5'} and R^{6'} of the "group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^{5'} and R^{6'} are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R^{5'} and R^{6'} may bind to each other to form a cyclic group together with the adjacent phosphorus atom" represented by R² include

- (1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C₃₋₇ cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted alkynyl (e.g. C₂₋₁₀ alkynyl such

as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-pentyne, 3-hexynyl, etc., preferably lower (C_{1-6}) alkynyl, etc.);

(6) an optionally substituted aralkyl (e.g. phenyl- C_{1-4} alkyl (e.g. benzyl, phenethyl, etc.), etc.);

5 (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl,
10 (4) optionally substituted cycloalkenyl, (5) optionally substituted alkynyl, (6) optionally substituted aralkyl and (7) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl
15 group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g.
20 methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the "optionally substituted hydroxy group" represented by R^5 and R^6 include a hydroxy group which may have

25 (1) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

30 (2) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(3) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably
35 lower (C_{2-6}) alkenyl, etc.);

(4) an optionally substituted cycloalkenyl (e.g. C_{3-7}

- cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted aralkyl (e.g. phenyl-C₁₋₄ alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- 5 (6) an optionally substituted acyl (e.g. C₂₋₄ alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.
- 10

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and

15 (7) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the

20 number of the substituents are preferably 1 to 3.

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In the above formula, the groups R^{5'} and R^{6'} may bind to each other to form a cyclic group (preferably, 5- to 7-membered ring) together with the adjacent phosphorus atom. Said cyclic group may have a substituent. Examples of the

30 substituent include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₂₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl

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(e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

In the above formula (I'), examples of the counter anion, when the phosphorus atom forms a phosphonium, include an anion of a halogen atom (e.g. Cl⁻, Br⁻, I⁻, etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others, Cl⁻, Br⁻, I⁻, etc. are preferable.

Examples of the optionally substituted amino group represented by R^{5'} and R^{6'} include an amino group which may have 1-2 substituents selected from

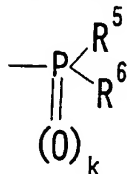
- (1) an optionally substituted alkyl (e.g. C₁₋₁₀ alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C₁₋₆) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C₃₋₇ cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C₂₋₁₀ alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C₂₋₆) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C₃₋₇ cycloalkenyl such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc., etc.);
- (5) an optionally substituted acyl (e.g. C₂₋₄ alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);

(6) an amino group which may have 1-2 optionally substituted aryl groups (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituent, which the above mentioned

- (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C₁₋₄ alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C₁₋₄ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C₁₋₄ alkanoyl (e.g. acetyl, propionyl, etc.), C₁₋₄ alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

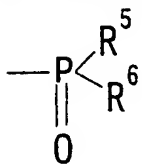
- As the group R², (1) an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom and (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R⁵ and R⁶ are independently an optionally substituted hydrocarbon group or an optionally substituted amino group, and R⁵ and R⁶ may bind to each other to form a cyclic group together with the adjacent phosphorus atom are preferable.

- As the group R², (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing

heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group of the formula:



5

wherein R⁵ and R⁶ are independently an optionally substituted hydrocarbon group, and R⁵ and R⁶ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, etc. are more preferable.

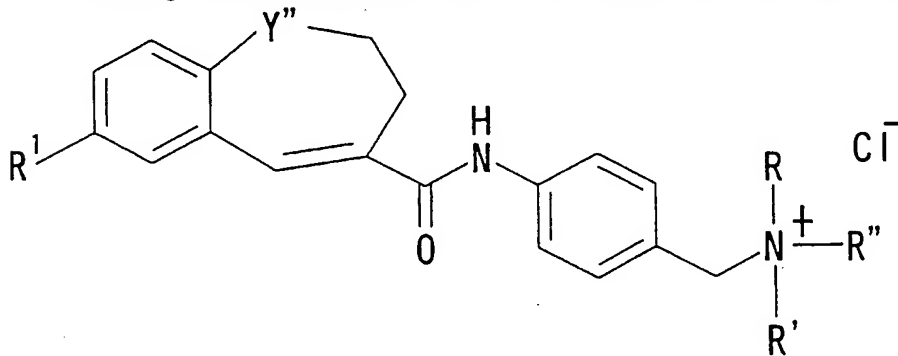
10

As the group R⁷, (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium is preferable, and a group of the formula:

-N⁺RR'R" wherein R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group is more preferable.

15

Among the Compound (I'), a compound of the formula:



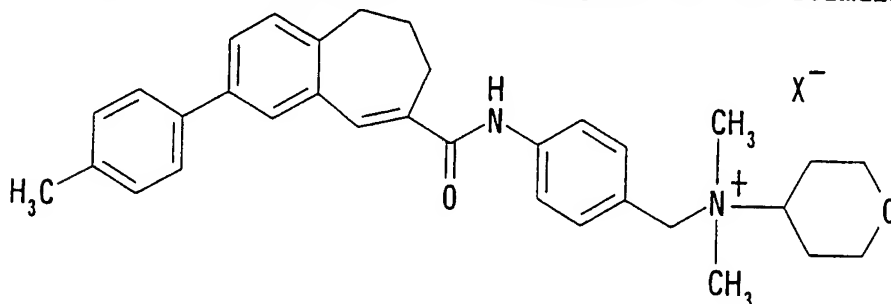
wherein R¹ is an optionally substituted benzene or an optionally substituted thiophene; Y'' is -CH₂-, -S- or -O-; and R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group is preferable.

25

Examples of the "optionally substituted aliphatic

hydrocarbon group" and the "optionally substituted alicyclic heterocyclic ring group" represented by R, R' or R" include those exemplified by the substituents for the "optionally substituted amino" represented by R¹. Among them, as the group R or R', an optionally substituted acyclic hydrocarbon group is preferable, an optionally substituted C₁₋₆ alkyl group is more preferable, and methyl is most preferable; and as the group R", an optionally substituted alicyclic hydrocarbon group (more preferably, an optionally substituted C₃₋₈ cycloalkyl group; further more preferably, an optionally substituted cyclohexyl) or an optionally substituted alicyclic heterocyclic ring group (more preferably, an optionally substituted saturated alicyclic heterocyclic ring group (preferably 6-membered ring group); further more preferably, an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl; most preferably, an optionally substituted tetrahydropyranyl) is preferable.

Among the Compound (I'), a compound of the formula:



wherein X⁻ is an anion is preferable.

Examples of the anion include that of a halogen atom; that derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; that derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; that

derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others, an anion of a halogen atom is preferable.

Among the Compound (I'), the following compounds and
5 their salts are preferable:

N-methyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-
piperidinium iodide;

10 N-methyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]piperidinium
iodide;

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide;

15 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide;

7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-
20 carboxamide;

N,N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium iodide;

25 N,N-dimethyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(4-oxocyclohexyl)ammonium chloride;

N,N-dimethyl-N-[4-[[[7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium chloride; etc.

30

Examples of the salts of the compound represented by the formula (I') include a pharmaceutically acceptable salt such as a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt
35 with basic or acidic amino acid, etc. Examples of the salt with the inorganic base include a salt with alkali metal

(e.g. sodium, potassium, etc.), alkaline earth metal (e.g. calcium, magnesium, etc.), aluminum, ammonium, etc.

Examples of the salt with the organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.

Examples of the salt with the inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Examples of the salt with the organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Examples of the salt with the basic amino acid include a salt with arginine, lysine, ornithine, etc.

Examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid, etc.

The compound of the formula (I') of the present invention may be hydrated or solvated. When the compound of the formula (I') of the present invention exists as configuration isomer, diastereomer, conformer, etc., it is possible to isolate individual isomers with per se known separation and purification method, if desired. When the compound of the formula (I') of the present invention is racemate, it can be separated into (S)-compound and (R)-compound with usual optical resolution and individual optical isomers and a mixture thereof are included in the scope of the present invention.

The present compound of the formula (I') or a salt thereof (hereinafter, "Compound (I')") include the compound of the formula (I') and its salt; and also a compound of the formula (I) and its salt) alone or as an admixture with a pharmaceutically acceptable carrier (e.g. solid formulations such as tablets, capsules, granules, powders, etc.; liquid formulations such as syrups, injections, etc.) may be orally or non-orally administered.

Examples of non-oral formulations include injections, drops, suppositories, pessaries, etc. In particular, pessary is useful for the prophylaxis of infectious disease of HIV.

- 5 Examples of the carriers include various organic or inorganic carriers which are generally used in this field. For example, an excipient, a lubricant, a binder, an disintegrating agent, etc. are used in the solid formulations, and a solvent, a solubilizer, a suspending agent, a
10 isotonizing agent, a buffer, a soothing agent, etc. are used in the liquid formulations. In addition, if desired, an appropriate additive such as a preservative, an antioxidant, a colorant, a sweetener, etc. may be used in the above formulations.
- 15 Examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silic acid anhydride, etc. Examples of the lubricant include
20 magnesium stearate, calcium stearate, talc, colloidal silica, etc. Examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl
25 cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, etc. Examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, sodium
30 carboxymethyl starch, etc. Examples of the solvent include water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, etc. Examples of the solubilizer include polyethyleneglycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol,
35 triethanolamine, sodium carbonate, sodium citrate, etc. Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate, etc.;
- hydrophilic polymers such as polyvinylalcohol, polyvinylpyrrolidone, sodium carboxymethyl cellulose,

5 methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.; etc. Examples of the isotonizing agent include sodium chloride, glycerin, D-mannitol, etc. Examples of the buffer include a buffer solution of phosphate, acetate, carbonate, citrate, etc. Examples of the soothing agent include benzylalcohol, etc. Examples of the preservative include paraoxybenzoic acid esters, chlorobutanol, benzylalcohol, phenethylalcohol, dehydroacetic acid, sorbic acid, etc. Examples of the antioxidant include sulfites, ascorbic acid, etc.

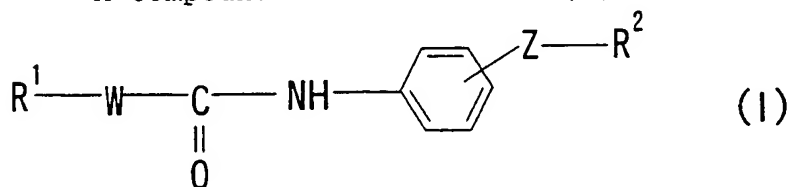
10 The compound of the formula (I') or a salt thereof of the present invention may be used in combination with other drug for the treatment or prophylaxis of infectious disease of HIV (in particular, a pharmaceutical composition for the treatment or prophylaxis of AIDS). In this case, these drugs can be formulated by mixing individually or simultaneously with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, which can be administered orally or non-orally as a pharmaceutical composition for the treatment or prophylaxis of infectious disease of HIV. In the case of formulating these effective components individually, while the individually formulated agents can be administered in the form of their mixture prepared by using e.g. a diluent when administered, the individually formulated agents can also be administered separately or simultaneously or with time intervals to the one and same subject. A kit for administering the individually formulated effective components in the form of their mixture prepared by using e.g. a diluent when administered (e.g. a kit for injection which comprises two or more ampoules each comprising a powdery component and a diluent for mixing and dissolving two or more components when administered, etc.), a kit for administering the individually formulated agents simultaneously or with time intervals to the one and the same subject (e.g. a kit for tablets to be administered simultaneously or with time

intervals, characterized by having two or more tablets each comprising an agent and said tablets being put in one or separate bags and, if necessary, a column to describe time to be administered each agent, etc.), etc. are also included
 5 by the pharmaceutical composition of the present invention.

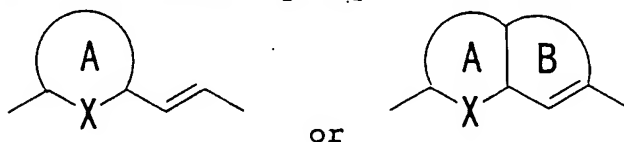
Example of the other pharmaceutical agent for the treatment or prophylaxis of infectious disease of HIV to be used in combination with the compound of the formula (I') or a salt thereof of the present invention include nucleotide
 10 reverse transcriptases inhibitor such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil, etc.; non-nucleotide reverse transcriptases inhibitor (including an agent having anti-oxidation activity such as immunocal,
 15 oltipraz, etc.) such as nevirapine, delavirdine, efavirenz), loviride, immunocal, oltipraz, etc.; protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir, etc.; etc.

As the nucleotide reverse transcriptase inhibitor,
 20 zidovudine, didanosine, zalcitabine, lamivudine, stavudine, etc. are preferable; as the non-nucleotide reverse transcriptase inhibitor, nevirapine, delavirdine, etc. are preferable; and as the protease inhibitor, saquinavir, ritonavir, indinavir, nelfinavir, etc. are preferable.

25 A compound of the formula (I):

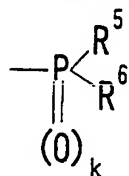


wherein R¹ is an optionally substituted 5- to 6-membered ring, W is a divalent group of the formula:



30 (wherein the ring A is an optionally substituted 5- to

6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring), Z is a chemical bond or a divalent group, and R² is (1) an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; R⁵ and R⁶ are independently an optionally substituted hydrocarbon group or an optionally substituted amino group, and R⁵ and R⁶ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof is a novel compound, and the production method thereof is described below.

The compound of the formula (I) or a salt thereof can be produced in accordance with per se known methods, for example, the methods described below, the methods described in JP-A-73476/1996, or analogous methods thereto.

A salt of the compound of the formulas (I), (II), (III), (IV), (V), (I-1), (I-2) and (I-3) may be similar to that of the compound the formula (I').

In the following reaction steps, when the starting compounds have, as substituents, an amino group, a carboxyl group and/or hydroxy group, these groups may be protected by ordinary protective groups such as those generally employed in peptide chemistry, etc. After the reaction, if necessary, the protective groups may be removed to obtain

the desired compound.

Examples of the amino-protective group include an optionally substituted C₁₋₆ alkylcarbonyl (e.g. formyl, methylcarbonyl, ethylcarbonyl, etc.), phenylcarbonyl, C₁₋₆ alkyloxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, etc.), aryloxycarbonyl (e.g. phenoxycarbonyl, etc.), C₇₋₁₀ aralkyloxycarbonyl (e.g. benzyloxycarbonyl, etc.), trityl, phthaloyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkylcarbonyl (e.g. acetyl, propionyl, butyryl, etc.), nitro group, etc.

Examples of the carboxyl-protective group include an optionally substituted C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, silyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkylcarbonyl (e.g. formyl, acetyl, propionyl, butyryl, etc.), nitro group, etc.

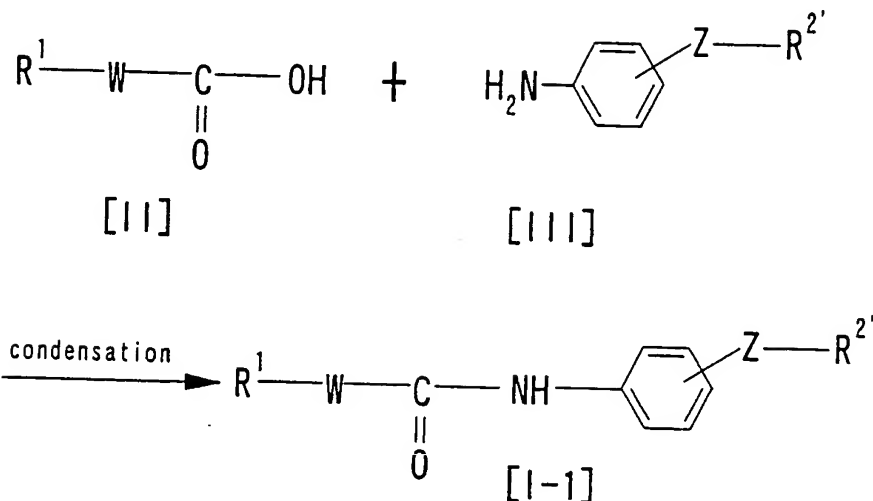
Examples of the hydroxy-protective group include an optionally substituted C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C₇₋₁₀ aralkyl (e.g. benzyl, etc.), C₁₋₆ alkylcarbonyl (e.g. formyl, acetyl, propionyl, etc.), phenyloxycarbonyl, C₇₋₁₀ aralkyloxycarbonyl (e.g. benzyloxycarbonyl, etc.), pyranyl, furanyl, silyl, etc. These protective groups may be substituted by 1 to 4 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl, phenyl, C₇₋₁₀ aralkyl, nitro group, etc.

These protective group may be introduced or removed by per se known methods (e.g. a method described in Protective Groups in Organic Chemistry (J. F. W. McOmie et al.; Plenum Press Inc.) or the methods analogous thereto.

For example, employable method for removing the protective groups is a method using an acid, a base, reduction, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-

methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.

[Method A]



5 herein each symbol is as defined above. W

This production method is carried out by reacting the compound [II] with the aniline derivative [III] to obtain the anilide Compound [I-1].

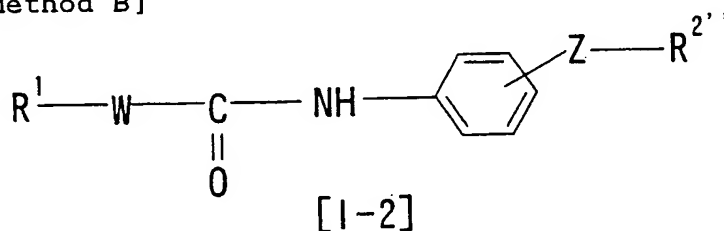
10 The condensation reaction of the compounds [II] and [III] is carried out by usual methods for peptide synthesis. Said methods for peptide synthesis are employed according to optional known methods, for example, methods described in "Peptide Synthesis" written by M. Bodansky and M. A. Ondetti, Interscience, New York, 1966; "The Proteins",
 15 volume 2, written by F. M. Finn and K. Hofmann, H. Nenrath and R. L. Hill edition, Academic Press Inc., New York, 1976; "peputido-gosei no kiso to jikken (Basis and Experiment of Peptide Synthesis)" written by Nobuo Izumiya et al., Maruzen
 20 K.K., 1985; etc., as well as azide method, chloride method, acid anhydride method, mixed acid anhydride method, DCC method, active ester method, method using Woodward reagent K, carbonyldiimidazole method, oxidation-reduction method, DCC/HONB method, etc. and in addition WSC method, method

using diethyl cyanophosphate (DEPC), etc.

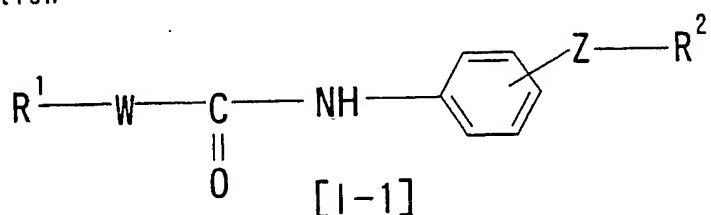
The condensation reaction can be carried out in a solvent. Examples of the solvents to be employed in the reaction include anhydrous or hydrous N,N-dimethylformamide (DMF), dimethylsulfoxide, pyridine, chloroform, dichloromethane, tetrahydrofuran, dioxane, acetonitrile, or a suitable mixture of these solvents. The reaction temperature is generally about -20°C to about 50°C, preferably about -10°C to about 30°C and the reaction time is generally about 1 to about 100 hours, preferably about 2 to about 40 hours.

The thus obtained anilide derivative [I-1] can be isolated and purified by known separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, recrystallization, solvent convert, chromatography, etc.

[Method B]



- ① ammoniumation
 - ② tertiary amination
-
- ③ reductive amination, or
 - ④ oxidation



- ① When the group R^{2''} in Compound [I-2] is, for example, a tertiary amine residue, Compound [I-1] wherein the group R^{2'} is a quaternary ammonium can be produced by reacting

- Compound [I-2] with halogenated alkyl or halogenated aralkyl. Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 5 moles of the halogenated alkyl (e.g. halogenated lower (C_{1-6}) alkyl, etc.) or halogenated
- 5 aralkyl (e.g. halogenated lower (C_{1-6}) alkyl-phenyl, etc.) is used per mole of Compound [I-2]. The reaction is carried out in an inert solvent such as toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide, dimethylacetamide, etc., or a suitable
- 10 mixture of these solvents. The reaction temperature is generally about 10°C to about 160°C , preferably about 20°C to about 120°C and the reaction time is generally about 1 hour to about 100 hours, preferably about 2 hours to about 40 hours. This reaction is preferably carried out under
- 15 inert gas (e.g. nitrogen, argon, etc.) atmosphere.
- ② When the group $R^{2'}$ in Compound [I-2] is, for example, a secondary amine residue, Compound [I-1] wherein the group $R^{2'}$ is a tertiary amino can be produced by reacting Compound [I-2] with halogenated alkyl or halogenated aralkyl.
- 20 Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 2 moles of the halogenated alkyl or halogenated aralkyl is used per mole of Compound [I-2]. If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as
- 25 triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc.
- 30 This tertiary amination reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethylether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane,
- 35 dimethylformamide (DMF), dimethylsulfoxide (DMSO), pyridine, etc., or a suitable mixture of these solvents.

The reaction temperature is generally about 0°C to 180°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

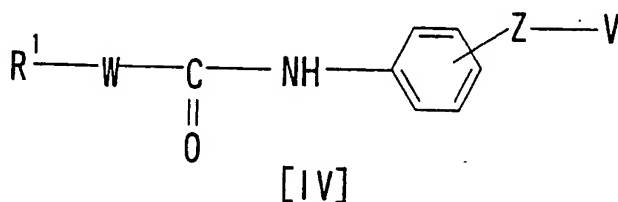
- 5 ③ When the group R²" in Compound [I-2] is, for example, a secondary amine residue, Compound [I-1] wherein the group R²' is a tertiary amino can be produced by reacting Compound [I-2] with aldehyde compound in the presence of a reductive amination reagent such as triacetoxysodium boron hydride, cyanosodium boron hydride, sodium boron hydride, etc.

10 The conditions of this reductive amination reaction varies depending on the reagent to be used. For example, when triacetoxysodium boron hydride is used, reaction is carried out in an inert solvent such as dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethylether, dioxane, acetonitrile, dimethylformamide (DMF), etc., or a suitable mixture of these solvents. In this case, about 1 to 2 moles of the reagent is used per mole of Compound [I-2]. The reaction temperature is

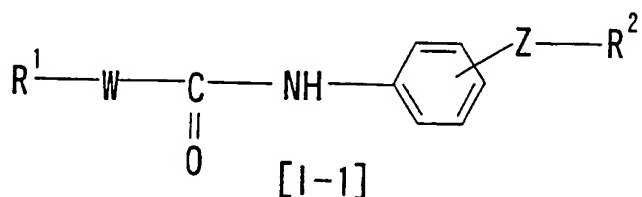
15 generally about 0°C to about 80°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

- 20 ④ When the group R²" in Compound [I-2] is, for example, a sulfide residue or a tertiary amine residue, Compound [I-1] wherein the group R²' is a sulfinyl group, a sulfonyl group or an amine oxide group can be produced by reacting Compound [I-2] with an oxidizing agent such as m-chloroperbenzoic acid, perbenzoic acid, p-nitroperbenzoic acid, magnesium
- 25 monoperoxyphthalate, peracetic acid, hydrogen peroxide, sodium periodate, potassium periodate, etc. The conditions of this oxidation reaction varies depending on the oxidizing agent to be used. For example, when m-chloroperbenzoic acid is used, reaction is carried out in an inert solvent such
- 30 as dichloromethane, chloroform, 1,2-dichloroethane, diethylether, tetrahydrofuran, acetone, ethyl acetate.
- 35

etc., or a suitable mixture of these solvents. Usually, about 1-3 moles of oxidizing agent is used per mole of Compound [I-2]. The reaction temperature is generally about -25°C to about 80°C (preferably -25°C to 25°C), and the reaction time is generally about 1 hour to about 40 hours. [Method C]



① ammoniumation
② phosphoniumation or
③ substitution



wherein V in the Compound [IV] is a halogen atom (chlorine, bromine, iodine, etc.), or a sulfonyloxy group (methanesulfonyloxy group, trifluoromethanesulfonyloxy group, benzenesulfonyloxy group, toluenesulfonyloxy group, etc.), and the other symbols are as defined above.

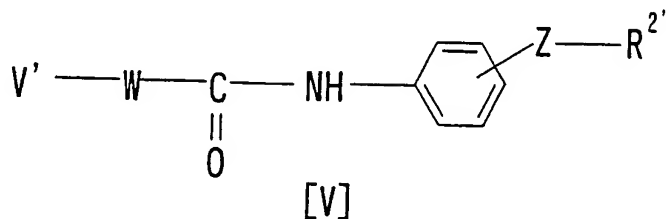
① Compound [I-1] wherein the group R^{2'} is a quaternary ammonium can be produced by reacting Compound [IV] and a tertiary amine. The reaction is carried out in an inert solvent such as toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylacetamide, etc., or a suitable mixture of these solvents. Usually, about 1-3 moles of the tertiary amine is used per mole of Compound [IV]. The reaction temperature is generally about 10°C to about 120°C, and the reaction time

is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

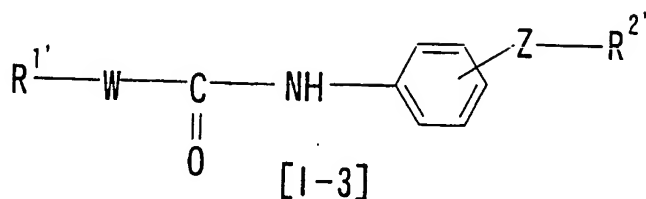
- ② Compound [I-1] wherein the group $R^{2'}$ is a quaternary phosphonium can be produced by reacting Compound [IV] and a tertiary phosphine. The reaction is carried out in an inert solvent such as toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, dimethylformamide (DMF), or a suitable mixture of these solvents. Usually, about 1-2 moles of the tertiary phosphine is used per mole of Compound [IV]. The reaction temperature is generally about 20°C to about 150°C, and the reaction time is generally about 1 hour to about 50 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.
- ③ Compound [I-1] wherein the group $R^{2'}$ is a secondary or tertiary amino group or a thio group can be produced by reacting Compound [IV] and primary or secondary amine compound or thiol compound. Usually, about 1 to 3 moles of the primary or secondary amine compound or the thiol compound is used per mole of Compound [IV]. If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc. This substitution reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethylether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylsulfoxide (DMSO), pyridine, etc., or a suitable mixture of these solvents. The reaction temperature is generally about -10°C to about 180°C, and the reaction time is generally about 1 hour to about 40 hours.

The reaction is carried out preferably under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

[Method D]



Suzuki reaction



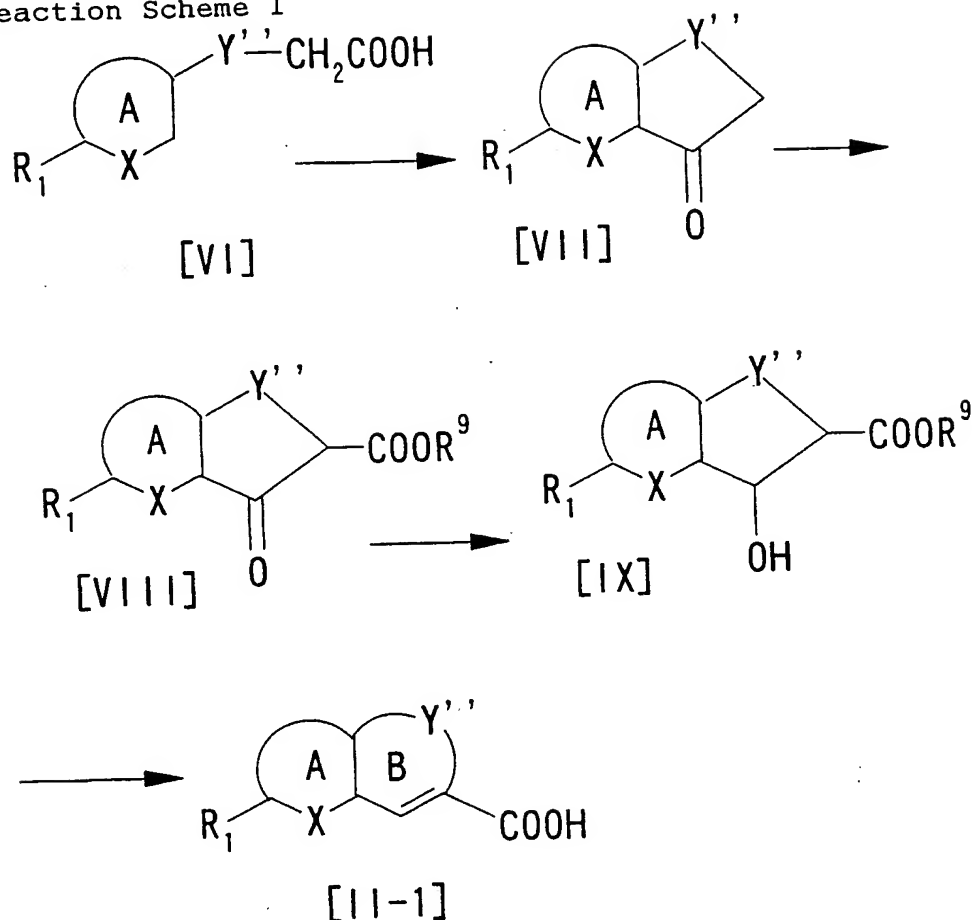
- 5 wherein V' is a halogen atom (bromine, iodine, etc.) or a sulfonyloxy group (trifluoromethanesulfonyloxy group, etc.), and the other symbols are as defined above.

- 10 Compound [I-3] wherein the group R^{1'} is a 5- to 6-membered aromatic ring group can be produced by subjecting Compound [V] to, for example, Suzuki reaction [cross condensation reaction of aryl borate with e.g. aryl halide or aryloxytrifluoromethanesulfonate in the presence of palladium catalyst; A. Suzuki et al., Synth. Commun. 1981,
15 11, 513]. Usually, about 1-1.5 times moles of aryl borate is used per mole of Compound [V].

- Compound [II] used as a starting material can be produced by a known method (e.g. method described in JP-A-73476/1996, etc.) or the methods analogous thereto.
20 For example, Compound [II] can be produced by a method described in the following Reaction Scheme I, a method described in the following Reference Examples or the methods

analogous thereto.

Reaction Scheme I



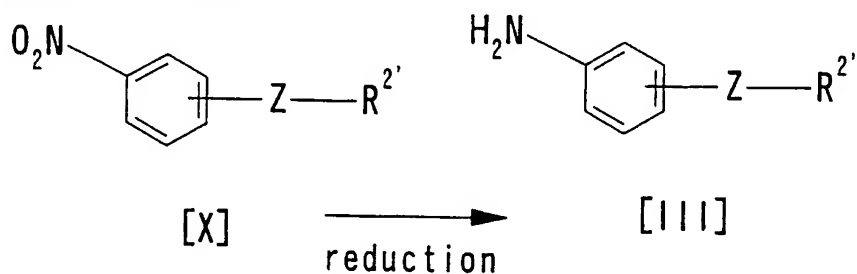
5 wherein R^9 is a C_{1-4} alkyl group, Y'' is a divalent group, which does not contain a unsaturated bond and by which the ring B forms a 5- to 7-membered ring, and the other symbols are as defined above.

10 In this reaction, the compound of the formula [VI] is heated with a polyphosphoric acid, or Compound [VI] is converted to acid chloride with thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, etc., followed by subjecting the resulting
15 acid chloride to usual Friedel-Crafts reaction and cyclizing

the same to produce Compound [VII]. Compound [VII] is reacted with carbonate ester in the presence of a base to produce ketoester [VIII]. Compound [VIII] is subjected to reduction with catalytic hydrogenation or sodium boron hydride, etc. to produce Compound [IX]. Compound [IX] is subjected to dehydration and ester hydrolysis by per se known method to produce unsaturated carboxylic acid [II-1].

Compound [III] can be produced by a known method (e.g. method described in JP-A-73476/1996, etc.) or the methods analogous thereto. For example, Compound [III] can be produced by a method described in the following Reaction Scheme II, a method described in the following Reference Examples or the methods analogous thereto.

15 Reaction Scheme II



The reduction of Compound [X] can be carried out per
se known methods, for example, reduction with metal,
reduction with metal hydride, reduction with metal hydride
20 complex compound, reduction with diborane or substituted
borane, catalytic hydrogenation, etc. That is, this
reaction is carried out by treating Compound [X] with
reduction agent. Examples of the reduction agent include
metal such as reduced iron, zinc powder, etc.; alkali metal
25 boron hydride (e.g. sodium boron hydride, lithium boron
hydride, etc.); metal hydride complex compound such as
aluminum lithium hydride, etc.; metal hydride such as sodium
hydride etc.; organic tin compound (triphenyltin hydride,
etc.), metal complex compound and metal salt such as nickel
30 compound, zinc compound etc.; catalytic reduction agent

using hydrogen and transit metal catalyst such as palladium, platinum, rhodium, etc.; diborane; etc. Among others, as the reduction agent, catalytic reduction agent using hydrogen and transit metal catalyst such as palladium, platinum, rhodium, etc.; reduced iron, etc. are preferable. The reaction is carried out in a solvent which does not affect the reaction. Examples of the solvent include benzene, toluene, xylene, chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, diethylether, tetrahydrofuran, dioxane, methanol, ethanol, propanol, isopropanol, 2-methoxyethanol, N,N-dimethylformamide, acetic acid, or a suitable mixture of these solvents, etc. The solvent is appropriately selected depending on kind of the reduction agent. The reaction temperature is generally about -20°C to about 150°C, preferably about 0°C to about 100°C, and the reaction time is generally about 1 to about 24 hours.

The resulting Compound [III] can be separated and purified with known separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, was recrystallized with, solvent conversion, chromatography, etc.

The compound of the formula (I') or a salt thereof of the present invention has potent CCR5 antagonistic activity and therefore can be used for the treatment or prophylaxis of various infectious diseases of HIV, for example, AIDS in human. The compound of the formula (I') or a salt thereof of the present invention is low toxic and safely used as CCR5 antagonist for the treatment or prophylaxis of AIDS and also for the prevention of the progression of AIDS.

The dose per day of the compound of the formula (I') or a salt thereof varies depending on the condition and body weight of a patient, administration route, etc. Typical daily dose per adult patient (body weight: 50Kg) for oral administration is about 5-1000mg, preferably about 10-600mg, more preferably about 10-300mg, and in particular about

15-150mg, as active ingredient [the compound of the formula (I') or a salt thereof] and the compound of the formula (I') or a salt thereof is administered once or 2-3 times par day.

5 When the compound of the formula (I') or a salt thereof is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor, the dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200-1/2 or more of usual
10 dose to about 2-3 times or less of usual dose. In case that two or more drugs are used in combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as
15 the dose when they are used alone.

Typical daily dose of the reverse transcriptase inhibitor and the protease inhibitor is as follows:

	zidovudine	: 100mg
	didanosine	: 125-200mg
20	zalcitabine	: 0.75mg
	lamivudine	: 150mg
	stavudine	: 30-40mg
	saquinavir	: 600mg
	ritonavi	: 600mg
25	indinavir	: 800mg
	nelfinavir	: 750mg

In case of combination use of the compound of the formula (I') or a salt thereof with a reverse transcriptase inhibitor and/or a protease inhibitor preferred embodiments
30 are shown below.

① A drug containing about 10-300mg of the compound of the formula (I') or a salt thereof and a drug containing about 50-200mg of zidovudine to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be
35 administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

- ② A drug containing about 10-300mg of the compound of the formula (I') or a salt thereof and a drug containing about 300-1200mg of saquinavir to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

Best Mode for Carrying out the Invention

The present invention is hereinafter described in more detail by means of the following Test Example, Reference Example and Working Example, which are mere examples of the present invention and are not construed as limitative to the present invention.

The following gene manipulation is carried out in accordance with methods described in textbook (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or protocol attached to reagents.

Test Example

(1) Cloning of human CCR5 chemokine receptor

Cloning of CCR5 gene was carried out by PCR (polymerase chain reaction) from human spleen cDNA. With using 0.5ng of spleen cDNA (Toyobo, QUICK-Clone cDNA) as template, PCR was performed in DNA Thermal Cycler 480 (Perkin-Elmer) (reaction conditions: 30 cycles of 95°C for 1 minute, 60°C for 1 minute, and 75°C for 5 minutes) by adding primer set, 5'-CAGGATCCGATG GATTATCAAGTGTCAAGTCCAA-3' (25pmol) and 5'-TCTAGATCACAAGCC CACAGATATTTCTGCTCC-3' (25pmol), which were designed referring to nucleotide sequence of CCR5 gene reported by Samson et al. (Biochemistry, 35(11), 3362-3367 (1996)) and by using TaKaRa EX Taq (Takara Shuzo). The resultant PCR product was subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment, which was subjected to Original TA Cloning Kit (Funakoshi) to carry out cloning of CCR5 gene.

(2) Preparation of plasmid for expression of human CCR5

The plasmid obtained in the above (1) was digested with

restriction enzymes XbaI (Takara Shuzo) and BamHI (Takara Shuzo) and subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment. The DNA fragment was mixed with plasmid pcDNA3.1 (Funakoshi) for expression in animal cells, said plasmid being digested with XbaI and BamHI, and they were ligated with DNA Ligation Kit Ver.2 (Takara Shuzo). The resulting plasmid was subjected to transformation of competent cell of E. coli JM109 (Takara Shuzo) to obtain plasmid pCKR5.

10 (3) Introduction of plasmid for expression of human CCR5 into CHO-K1 cell and Expression of said plasmid in CHO-K1 cell

CHO-K1 cells were grown in 750ml of tissue culture flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and took off with 0.5g/L trypsin-0.2g/L EDTA (Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown below. That is, to the cuvette of 0.4cm gap were added 8×10^6 cells and 10 μ g of plasmid pCKR5 for expression of human CCR5, and electroporation was carried out under 0.25kV of voltage and 960 μ F of capacitance. The cells were transferred into Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again took off and centrifuged, and suspended in Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum and 500 μ g/ml of geneticin (Life Tech Oriental). The suspension was diluted to give 10^4 cells/ml of the suspension, which was inoculated on 96 well plate (Becton Dickinson) to give geneticin resistant cells. The resulting geneticin resistant cells were cultivated in 96 well plate (Becton Dickinson), and cells expressing CCR5 were selected from the geneticin resistant cells. That is, in assay buffer (Ham's F12 medium containing 0.5% BSA and

20mM HEPES (Wako Pure Chemical, pH7.2) to which was added 200pM of [¹²⁵I]-RANTES (Amersham) as ligand, binding reaction was carried out at room temperature for 40 minutes, and the buffer was washed with cooled PBS. To the buffer was added 50 μ l/well of 1M NaOH, and the mixture was stirred. Radioactivity was determined with γ -counter to select CHO/CCR5 cells which specifically bind to the ligand.

(4) Evaluation of Test Compounds based on CCR5 antagonistic activity

The CHO/CCR5 were inoculated on 96 well microplate (5 \times 10⁴ cells/well) and cultivated for 24 hours. The medium was removed by means of suction, and to each well was added assay buffer containing Test Compound (1 μ M) and then 100pM of [¹²⁵I]-RANTES (Amersham) as ligand. Binding assay was carried out at room temperature for 30 minutes, and assay buffer was removed by means of suction. Each well was washed twice with cooled PBS, and 200 μ l of Microscint-20 (Packard Instrument, Inc.) was added to each well. Radio-activity was determined with Top-Count Micro Scintillation Counter (Packard Instrument, Inc.).

According to the method described above, inhibition rate of Test Compound (whose number is referred to in the following Examples) to CCR5 binding.

The results are shown in Table 1.

Table 1

Compound Number	Inhibition Rate (%)
16	88
92	100
96	93
97	94
100	100
128	87
180	99
209	80
248	99

249	96
250	96
<u>Ref Ex 51</u>	<u>73</u>

- 5 (5) Inhibitory effect on HIV-1 infection to MAGI-CCR5 cell
The plasmid where β -galactosidase gene was ligated
downstream of HIV-1 LTR was introduced into CD4 positive
HeLa cell, to which human CCR5 was further introduced to
obtain transformant MAGI-CCR5. By using said transformant
10 MAGI-CCR5, degree of HIV-1 infection was calculated from
 β -galactosidase activity (blue color due to decomposition
of 5-bromo-4-chloro-3-indolyl- β -D-galactopyranoside).
Specifically, MAGI-CCR5 cells were suspended in DMEM medium
containing 10% serum to prepare 5×10^4 cells/ml suspension.
15 To each well of 96 well plate was inoculated $200 \mu\text{l}$ of the
suspension, and the cells were cultivated at 37°C overnight.
The medium was removed by means of suction, and to the residue
was added $100 \mu\text{l}$ of the above medium containing $1.6 \mu\text{M}$ of
Test Compound 96 or $0.064 \mu\text{M}$ of Test Compound 248 and 100
20 μl of the above medium containing 300PFU of HIV-1 BA-L cells.
The cells were cultivated at 37°C for 2 days. The medium
was removed by means of suction. To the residue was added
 $200 \mu\text{l}$ of cell fixative (PBS containing 1% formaldehyde and
0.2% glutaraldehyde), and the mixture was allowed to stand
25 at room temperature for 5 minutes and washed twice with PBS.
To the mixture was added $100 \mu\text{l}$ of staining solution (PBS
containing $4 \mu\text{M}$ potassium ferrocyanide, $4 \mu\text{M}$ potassium
ferricyanide, $2 \mu\text{M}$ MgCl_2 and 0.4mg/ml X-gal), and the
mixture was allowed to stand at 37°C for 50 minutes and washed
30 twice with PBS. The number of blue cells was counted by
microscope and defined as the number of cells infected with
HIV-1. According to this method, inhibition rate on HIV-1
infection was determined and found that Compounds 96 and
248 respectively show 92% and 100% inhibition on HIV-1
35 infection.
- 6 (6) Inhibitory effect on HIV-1 infection to human PBMC

From normal person human peripheral blood mononuclear cells (PBMC) were separated, and the cells were stimulated with 10 μ g/ml of PHA (Phytohemagglutinin) and 20U/ml of interleukin-2 (IL-2) for 3 days. The cells were suspended in RPMI-1640 medium containing 20% serum to prepare 1×10^6 /ml suspension. To the suspension were infected HIV-1 BA-L cells (20ng as an amount of p24 antigen), and viruses were absorbed at 37°C for 2 hours. The cells were washed and suspended in RPMI-1640 medium containing 20% serum and IL-2 20U/ml to prepare 1×10^5 /ml suspension. To the PBMC suspension was added the same amount of a solution which contains 2.0 μ M of Test Compound 96 or 0.32 μ M of Test Compound 248, and the cells were cultivated at 37°C for 7 days in carbon dioxide gas incubator. The amount of p24 antigen in supernatant of the cultivated medium was determined by enzyme-linked immunosorbent assay (ELISA) and defined as degree of HIV-1 infection. According to this method, inhibition rate on HIV-1 infection was determined and found that Compounds 96 and 248 respectively show 96% and 74% inhibition on HIV-1 infection.

The pharmaceutical composition for antagonizing CCR5 (e.g. a medicament for the treatment or prophylaxis of infectious disease of HIV, a medicament for the treatment or prophylaxis of AIDS, etc.) comprising the compound of the formula (I') or a salt thereof of the present invention, as an active ingredient, can be prepared, for example, by the following prescriptions:

1. Capsule		
(1) Compound obtained in Working Example 128		40mg
(2) lactose		70mg
(3) fine crystalline cellulose		9mg
(4) magnesium stearate		1mg
	1 capsule	120mg

(1), (2), (3) and 1/2 of (4) are mixed and then granulated. To the granules is added the remainder of (4), and the whole is filled into a gelatin capsule.

2. Tablet

- | | |
|----------------------------------------------|-------|
| (1) Compound obtained in Working Example 128 | 40mg |
| (2) lactose | 58mg |
| (3) corn starch | 18mg |
| 5 (4) fine crystalline cellulose | 3.5mg |
| (5) magnesium stearate | 0.5mg |
| 1 tablet 120mg | |

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the mixture to compression molding.

3. Injection

A mixture of Compound obtained in Working Example 248 (500mg), mannitol (1000mg) and polysorbate 80 (100mg) is dissolved in distilled water (10ml), and to the solution is added distilled water to make the whole volume 20ml. The solution is filtered under sterile conditions. Each 2ml of the solution is filled into a vial for injection under sterile conditions.

20 Working Example

Reference Example 1

In THF (50ml) was dissolved 4-nitrobenzylchloride (5.00g), and piperidine (6.20g) was added to the mixture. The reaction mixture was stirred at room temperature for 25 20 hours. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was separated and purified with 30 column chromatography (ethyl acetate/hexane= 1/2) to give 1-(4-nitrobenzyl)piperidine (6.41g) as pale yellow oil. ¹H NMR (200MHz, CDCl₃) δ: 1.38-1.70 (6H, m), 2.30-2.45 (4H, m), 3.55 (2H, s), 7.51 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz).

35 Reference Example 2

In ethanol(50ml) was dissolved 1-(4-nitrobenzyl)-

piperidine (6.41g), and 10% dried palladium on carbon (0.33g) was added to the mixture. Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 24 hours. The palladium was
5 filtered off, and the filtrate was concentrated. The residue was recrystallized from hexane to give 1-(4-amino-benzyl)piperidine (1.01g) as pale yellow crystals.
mp 87-88°C

Elemental Analysis for $C_{12}H_{16}N_2$

10 Calcd: C, 75.74; H, 9.53; N, 14.72.

Found: C, 75.82; H, 9.58; N, 14.61.

IR (KBr) cm^{-1} : 3417, 2935, 1614, 1518, 1290, 1117, 1038, 991

1H NMR (200MHz, $CDCl_3$) δ : 1.35-1.65 (6H, m), 2.28-2.45 (4H, m), 3.37 (2H, s), 3.61 (2H, br s), 6.64 (2H, d, $J=8.6Hz$),

15 7.09 (2H, d, $J=8.6Hz$).

Reference Example 3

In THF (3ml) was dissolved 7-cyclohexyl-3,4-dihydro-naphthalene-2-carboxylic acid (100mg), and oxalyl chloride (41 μ l) and a drop of DMF were added to the mixture. The
20 mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (3ml), and diethyl 4-aminobenzyl-phosphonate (99mg) and triethylamine (60 μ l) were added to the mixture at room temperature. The reaction mixture was
25 stirred at room temperature for 3 hours. To the mixture was added water (100ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was
30 separated and purified with column chromatography (ethyl acetate/hexane= 3/1) to give 7-cyclohexyl-N-[4-(diethoxyphosphoryl)benzyl]-3,4-dihydronaphthalene-2-carboxamide (85mg) as colorless crystals.
mp 169-170°C

35 Elemental Analysis for $C_{27}H_{34}NO_4P \cdot 0.2H_2O$

Calcd: C, 68.83; H, 7.32; N, 2.97.

Found: C, 68.83; H, 7.34; N, 3.00.

IR (KBr) cm^{-1} : 3301, 2927, 1670, 1591, 1522, 1317, 1227, 1136, 1053, 1026, 966

^1H NMR (200MHz, CDCl_3) δ : 1.05-1.95 (16H, m), 2.40-2.56 (1H, m), 2.60-2.73 (2H, m), 2.80-3.00 (2H, m), 4.00-4.22 (4H, m), 7.05-7.15 (3H, m), 7.31 (1H, s), 7.68-7.88 (5H, m).

Reference Example 4

In thionyl chloride (5.8ml) was dissolved 4-nitrobenzylphosphonic acid (1.50g), and a drop of DMF were added to the mixture. The mixture was refluxed for 5 hours, and thionyl chloride was evaporated under reduced pressure. The residue was dissolved in THF (15ml), and to the mixture was dropped a solution of ethylamine (excess amount) and pyridine (1.2ml) in acetonitrile (2ml) at -78°C . The reaction mixture was stirred at room temperature for 24 hours.

The precipitates was filtered off, and the filtrate was concentrated. The residue was separated and purified with column chromatography (ethyl acetate/methanol=5/1) to give N,N'-diethyl-p-(4-nitrobenzyl)-phosphondiamide (1.88g) as colorless crystals.

mp $102-103^\circ\text{C}$

Elemental Analysis for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3\text{P}$

Calcd: C, 48.71; H, 6.69; N, 15.49.

Found: C, 48.51; H, 6.40; N, 15.37.

IR (KBr) cm^{-1} : 3244, 2970, 1520, 1348, 1173, 1128, 966

^1H NMR (200MHz, $\text{DMSO}-d_6$) δ : 0.99 (6H, t, $J=7.1\text{Hz}$), 2.65-2.85 (4H, m), 3.11 (2H, d, $J=18.8\text{Hz}$), 3.99-4.15 (2H, m), 7.52 (2H, dd, $J=2.2, 8.6\text{Hz}$), 8.15 (2H, d, $J=8.6\text{Hz}$).

Reference Example 5

In ethanol (20ml) was dissolved N,N'-diethyl-p-(4-nitrobenzyl)phosphondiamide (1.71g), and 10% dried palladium on carbon (0.09g) was added to the solution. Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 72 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was recrystallized from

diisopropylether to give p-(4-aminobenzyl)-N,N'-diethylphosphondiamide (1.28g) as colorless crystals.

mp 109-111°C

Elemental Analysis for $C_{11}H_{16}N_2OP \cdot 0.1H_2O$

5 Calcd: C, 54.35; H, 8.46; N, 17.29.

Found: C, 54.39; H, 8.42; N, 17.00.

IR (KBr) cm^{-1} : 3205, 2968, 1518, 1408, 1182, 1122, 1074, 829, 785

10 1H NMR (200MHz, $CDCl_3$) δ : 1.10 (6H, t, $J=7.1Hz$), 1.95-2.10 (2H, m), 2.80-3.03 (6H, m), 3.30-3.90 (2H, br), 6.64 (2H, d, $J=8.4Hz$), 7.07 (2H, d, $J=8.4Hz$).

Reference Example 6

In xylene (450ml) was dissolved 7-methoxy-1-tetralone (50.0g) under argon atmosphere. To the mixture was added
15 aluminum chloride (75.7g), and the mixture was refluxed for 4.5 hours. The mixture was cooled to room temperature. To the mixture was added 3N hydrochloric acid (500ml), and the mixture was extracted with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The
20 residue was separated and purified with column chromatography (ethyl acetate) to give 7-hydroxy-1-tetralone (36.4g) as dark green crystals.

mp 162-163°C

25 1H NMR (200MHz, $CDCl_3$) δ : 2.02-2.20 (2H, m), 2.65 (2H, t, $J=6.6Hz$), 2.90 (2H, t, $J=6.0Hz$), 6.00-6.20 (1H, br), 7.04 (1H, dd, $J=2.8, 8.4Hz$), 7.16 (1H, d, $J=8.4Hz$), 7.61 (1H, d, $J=2.8Hz$).

Reference Example 7

In dichloromethane (500ml) were dissolved 7-
30 hydroxy-1-tetralone (15.0g) and triethylamine (38.9ml) under argon atmosphere, and to the mixture was added dropwise trifluoromethanesulfonic acid anhydride (15.6ml) at 0°C. The reaction mixture was stirred for 2 hours at 0°C, and to the mixture was added water (500ml). The organic layer
35 was separated, washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and

concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1/7) to give 7-(trifluoromethanesulfoxy)-1-tetralone (23.3g) as pale brown oil.

- 5 ¹H NMR (200MHz, CDCl₃) δ : 2.10-2.25 (2H, m), 2.69 (2H, t, J=6.6Hz), 3.00 (2H, t, J=6.0Hz), 7.37 (2H, s), 7.91 (1H, s).

Reference Example 8

- A mixture of 7-(trifluoromethanesulfoxy)-1-tetralone (23.3g), phenyl borate (11.8g), potassium carbonate (21.9g), toluene (500ml), ethanol (50ml) and water (50ml) was stirred for 30 minutes at room temperature under argon atmosphere, and to the mixture was added tetrakis(triphenylphosphine)palladium (3.66g). The mixture was refluxed for 20 hours and then cooled to room temperature. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene/hexane=1/5/5) to give 7-phenyl-1-tetralone (15.1g) as pale brown oil.
- 15 ¹H NMR (200MHz, CDCl₃) δ : 2.10-2.25 (2H, m), 2.65-2.75 (2H, m), 2.96-3.05 (2H, m), 7.31-7.50 (4H, m), 7.57-7.67 (2H, m), 7.73 (1H, dd, J=2.2, 8.0Hz), 8.30 (1H, d, J=2.2Hz).
- 20

25 Reference Example 9

- A mixture of sodium methoxide (18.3g), dimethyl carbonate (107ml) and 7-phenyl-1-tetralone (15.1g) was refluxed for 30 minutes. The reaction mixture was cooled to 0°C. To the mixture was gradually added 3N hydrochloric acid (200ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give a brown solid. The solid was dissolved in dichloromethane (100ml), and to the mixture was added sodium boron hydride (1.60g) at 0°C.
- 35 To the mixture was added dropwise methanol (10ml) for 30

minutes, and the reaction mixture was stirred for 4 hours at 0°C. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in methanol (45ml). To the mixture was added 2N sodium hydroxide (50ml), and the mixture was refluxed for 2 hours. The reaction mixture was cooled to room temperature, acidified with concentrated hydro-chloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in Diglyme (1,1'-oxybis[2-methoxyethane]) (50ml), and to the mixture was added concentrated hydrochloric acid (10ml). The mixture was stirred for 2 hours at 100°C, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution and concentrated under reduced pressure. The residue was dissolved in 1N sodium hydroxide (200ml), washed with diethylether, acidified by adding concentrated hydrochloric acid to the aqueous layer and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol-water to give 7-phenyl-3,4-dihydronaphthalene-2-carboxylic acid (7.47g) as brown crystals.

mp 204-208°C

¹H NMR (200MHz, CDCl₃) δ: 2.61-2.73 (2H, m), 2.88-3.00 (2H, m), 7.23-7.60 (8H, m), 7.74 (1H, s).

Reference Example 10

In THF (250ml) was dissolved 4-nitrobenzylbromide (25.0g), and to the mixture was added morpholine (25.2ml) at 0°C. The reaction mixture was stirred for 15 hours at

room temperature. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate) to give 4-(4-nitrobenzyl)morpholine (25.5g) as pale yellow crystals. A portion of the crystals was recrystallized from diisopropylether to give pale yellow crystals which were used for various analyses. mp 79-80°C

Elemental Analysis for $C_{11}H_{14}N_2O_3$
Calcd: C, 59.45; H, 6.35; N, 12.60.
Found: C, 59.68; H, 6.25; N, 12.75.
IR (KBr) cm^{-1} : 3350, 1518, 1344, 1111, 1009, 864, 744
 1H NMR (200MHz, $CDCl_3$) δ : 2.37-2.55 (4H, m), 3.59 (2H, s), 3.65-3.80 (4H, m), 7.53 (2H, d, $J=8.4Hz$), 8.18 (2H, d, $J=8.4Hz$).

Reference Example 11

In ethanol (300ml) was dissolved 4-(4-nitrobenzyl)-morpholine (25.8g), and to the mixture was added dried 10% palladium on carbon (Pd-C) (1.00g). Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 20 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was separated and purified with column chromatography (ethyl acetate) to give 4-(4-aminobenzyl)-morpholine (430mg) as pale yellow crystals. mp 98-99°C

Elemental Analysis for $C_{11}H_{16}N_2O$
Calcd: C, 68.72; H, 8.39; N, 14.57.
Found: C, 68.57; H, 8.25; N, 14.59.
IR (KBr) cm^{-1} : 3350, 2804, 1635, 1516, 1282, 1111, 1005, 860
 1H NMR (200MHz, $CDCl_3$) δ : 2.32-2.52 (4H, m), 3.39 (2H, s), 3.45-3.80 (6H, m), 6.64 (2H, d, $J=8.2Hz$), 7.09 (2H, d, $J=8.2Hz$).

Reference Example 12

In THF (250ml) was dissolved 4-nitrobenzyl bromide (25.0g), and to the mixture was added pyrrolidine (24.1ml) at 0°C. The reaction mixture was stirred at room temperature for 60 hours. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate) to give 1-(4-nitrobenzyl)pyrrolidine (23.5g) as orange oil.
¹H NMR (200MHz, CDCl₃) δ: 1.75-1.85 (4H, m), 2.43-2.58 (4H, m), 3.71 (2H, s), 7.51 (2H, d, J=8.6Hz), 8.18 (2H, d, J=8.6Hz).

Reference Example 13

In ethanol (100ml) was dissolved 1-(4-nitrobenzyl)-pyrrolidine (23.5g), and to the mixture was added dried 10% palladium on carbon (1.00g). Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 20 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was separated and purified with column chromatography (ethyl acetate/triethylamine =10/1) to give 1-(4-aminobenzyl)pyrrolidine (8.54g) as orange oil.
¹H NMR (200MHz, CDCl₃) δ: 1.60-1.90 (4H, m), 2.35-2.55 (4H, m), 3.45-3.70 (4H, m), 6.64 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).

Reference Example 14

In THF (250ml) was dissolved 4-nitrobenzyl bromide (25.0g), and to the mixture was added 50% dimethylamine solution (29ml) at 0°C. The reaction mixture was stirred at room temperature for 60 hours. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl

acetate) to give dimethyl-4-nitrobenzylamine (20.7g) as orange oil.

¹H NMR (200MHz, CDCl₃) δ : 2.26 (6H, s), 3.52 (2H, s), 7.50 (2H, d, J=8.8Hz), 8.19 (2H, d, J=8.8Hz).

5 Reference Example 15

In ethanol (100ml) was dissolved dimethyl-4-nitrobenzylamine (20.7g), and to the mixture was added dried 10% palladium on carbon (1.00g). Under hydrogen atmosphere, the mixture was stirred at room temperature under
10 atmospheric pressure for 20 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was separated and purified with column chromatography (ethyl acetate) to give 4-aminobenzyl-dimethylamine (8.75g) as pale yellow oil.

15 ¹H NMR (200MHz, CDCl₃) δ : 2.21 (6H, s), 3.31 (2H, s), 3.53-3.70 (2H, br), 6.65 (2H, d, J=8.4Hz), 7.08 (2H, d, J=8.4Hz).

Reference Example 16

In THF (250ml) was dissolved 3-nitrobenzyl chloride
20 (25.0g), and to the mixture was added piperidine (36ml). The reaction mixture was stirred at room temperature for 20 hours. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried
25 with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate) to give 1-(3-nitrobenzyl)piperidine (32.2g) as pale yellow oil.

30 ¹H NMR (200MHz, CDCl₃) δ : 1.40-1.66 (6H, m), 2.33-2.44 (4H, m), 3.54 (2H, s), 7.47 (1H, t, J=8.0Hz), 7.67 (1H, d, J=8.0Hz), 8.10 (1H, d, J=8.0Hz), 8.20 (1H, s).

Reference Example 17

In ethanol (100ml) was dissolved 1-(3-nitrobenzyl)-piperidine (32.2g), and to the mixture was added dried 10%
35 palladium on carbon (1.61g). Under hydrogen atmosphere, the mixture was stirred at room temperature under

atmospheric pressure for 24 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was recrystallized from diisopropylether-hexane to give 1-(3-aminobenzyl)piperidine (15.8g) as colorless

5 crystals.

mp 109-110°C

Elemental Analysis for $C_{12}H_{16}N_2$

Calcd: C, 75.74; H, 9.53; N, 14.72.

Found: C, 75.81; H, 9.13; N, 14.87.

10 IR (KBr) cm^{-1} : 3398, 3184, 2948, 1643, 1606, 1454, 1302, 1101, 995, 795, 775, 698

1H NMR (200MHz, $CDCl_3$) δ : 1.35-1.65 (6H, m), 2.25-2.45 (4H, m), 3.38 (2H, s), 3.50-3.75 (2H, br), 6.57 (1H, br d, $J=7.9Hz$), 6.65-6.75 (2H, m), 7.08 (1H, t, $J=7.9Hz$).

15 Reference Example 18

In DMF (100ml) was dissolved 4-(2-bromoethyl)nitrobenzene (25.0g), and to the solution were added piperidine (12.9ml) and potassium carbonate (18.0g). The mixture was stirred at 70°C for 15 hours, and to the mixture was added
20 water (900ml), and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl
25 acetate) to give 1-[2-(4-nitro-phenyl)ethyl]piperidine (24.8g) as orange oil.

1H NMR (200MHz, $CDCl_3$) δ : 1.39-1.75 (6H, m), 2.35-2.65 (6H, m), 2.85-3.00 (2H, m), 7.36 (2H, d, $J=8.8Hz$), 8.14 (2H, d, $J=8.8Hz$).

30 Reference Example 19

In ethanol (100ml) was dissolved 1-[2-(4-nitro-phenyl)ethyl]piperidine (24.8g), and to the mixture was added dried 10% palladium on carbon (1.24g). Under hydrogen atmosphere, the mixture was stirred at room temperature
35 under atmospheric pressure for 86 hours. The palladium was filtered off, and the filtrate was concentrated to give

1-[2-(4-aminophenyl)ethyl]-piperidine (21.7g) as pale brown oil.

¹H NMR (200MHz, CDCl₃) δ : 1.40-1.80 (6H, m), 2.35-2.60 (6H, m), 2.60-2.80 (2H, m), 3.40-3.70 (2H, br), 6.62 (2H, d, J=8.4Hz), 7.00 (2H, d, J=8.4Hz).

Reference Example 20

In methanol (35ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (1.50g), and to the mixture was added concentrated sulfuric acid (0.1ml), and then the mixture was refluxed for 9 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100ml), and to the mixture was added activated manganese dioxide (9g). The mixture was refluxed for 48 hours and then cooled to room temperature. The manganese dioxide was filtered off, and the filtrate was concentrated. The residue was dissolved in methanol (15ml), and to the mixture was added 1N sodium hydroxide (10ml). The mixture was refluxed for 4 hours and then cooled to room temperature. The mixture was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-phenylnaphthalene-2-carboxylic acid (783mg) as colorless crystals.

mp 244-245°C

Elemental Analysis for C₁₇H₁₂O₂

Calcd: C, 82.24; H, 4.87.

Found: C, 82.10; H, 4.85.

IR (KBr) cm⁻¹: 3053, 1701, 1684, 1429, 1302, 860, 756, 696
¹H NMR (200MHz, CDCl₃) δ : 7.37-7.57 (3H, m), 7.70-7.77 (2H,

m), 7.86-8.02 (3H, m), 8.10-8.20 (2H, m), 8.77 (1H, s).

Reference Example 21

To a solution of 4-nitrobenzylalcohol (4.59g) in methanol (300ml) was added copper chloride (I) (17.8g) at room temperature, and then was gradually added potassium boron hydride (11.3g) for 40 minutes. The reaction mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=3/1) to give 4-aminobenzylalcohol (1.31g) as pale yellow crystals.

mp 53-55°C

Elemental Analysis for C_7H_9NO

Calcd: C, 68.27; H, 7.37; N, 11.37.

Found: C, 68.43; H, 7.43; N, 11.49.

IR (KBr) cm^{-1} : 3375, 3219, 1614, 1514, 1470, 1259, 1041, 854, 827, 748, 509

1H NMR (200MHz, $CDCl_3$) δ : 3.50-3.85 (2H, br), 4.56 (2H, s), 6.68 (2H, d, $J=8.4Hz$), 7.17 (2H, d, $J=8.4Hz$).

Reference Example 22

In THF (10ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (500mg), and to the solution were added oxalyl chloride (262 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in DMF (5ml), and to the mixture was dropwise added a solution of 4-aminobenzylalcohol (246mg) in pyridine (10ml) at 0°C. The reaction mixture was stirred at 0°C for 3 hours. To the mixture was added water (500ml), and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from

ethyl acetate-acetone to give N-[4-(hydroxymethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (486mg) as pale brown crystals.

mp 207-210°C

5 Elemental Analysis for $C_{21}H_{21}NO_2 \cdot 0.5H_2O$

Calcd: C, 79.10; H, 6.08; N, 3.84.

Found: C, 79.35; H, 5.97; N, 3.86.

IR (KBr) cm^{-1} : 3332, 1651, 1618, 1597, 1527, 1412, 1317, 831, 764, 700

10 1H NMR (200MHz, DMSO- d_6) δ : 2.50-2.66 (2H, m), 2.80-2.95 (2H, m), 4.46 (2H, s), 7.23-7.72 (13H, m), 9.91 (1H, s).

Reference Example 23

Under argon atmosphere, a mixture of 7-(trifluoromethanesulfoxy)-1-tetralone (9.02g), 4-methylphenyl borate (5.00g), potassium carbonate (8.46g), toluene (300ml), ethanol (30ml) and water (30ml) was stirred at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (1.06g). The mixture was refluxed for 14 hours. The reaction mixture was cooled to room temperature. The organic layer was separated, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene=1/10) to give 7-(4-methylphenyl)-1-tetralone (5.23g) as colorless crystals.

mp 86-87°C

Elemental Analysis for $C_{17}H_{16}O$

Calcd: C, 86.41; H, 6.82.

Found: C, 86.30; H, 6.69.

30 IR (KBr) cm^{-1} : 2947, 1682, 1606, 1489, 1435, 1323, 1223, 1178, 810

1H NMR (200MHz, $CDCl_3$) δ : 2.10-2.24 (2H, m), 2.39 (3H, s), 2.69 (2H, t, $J=6.6Hz$), 3.00 (2H, t, $J=6.0Hz$), 7.21-7.35 (3H, m), 7.52 (2H, d, $J=8.4Hz$), 7.71 (1H, dd, $J=2.2, 8.2Hz$), 8.27 (1H, d, $J=2.2Hz$).

Reference Example 24

Under argon atmosphere, a mixture of 7-(trifluoromethanesulfoxy)-1-tetralone (17.5g), 4-fluorophenyl borate (10.0g), potassium carbonate (16.6g), toluene (500ml), ethanol (50ml) and water (50ml) was stirred at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (2.08g). The mixture was refluxed for 14 hours. The reaction mixture was cooled to room temperature. The organic layer was separated, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene=1/10) to give 7-(4-fluorophenyl)-1-tetralone (13.8g) as brown oil. ¹H NMR (200MHz, CDCl₃) δ : 2.10-2.24 (2H, m), 2.70 (2H, t, J=6.6Hz), 3.01 (2H, t, J=6.0Hz), 7.07-7.19 (2H, m), 7.30 (1H, d, J=7.6Hz), 7.53-7.62 (2H, m), 7.67 (1H, dd, J=2.2, 8.2Hz), 8.23 (1H, d, J=2.2Hz).

Reference Example 25

A mixture of sodium methoxide (5.63g), dimethyl carbonate (33ml) and 7-(4-methylphenyl)-1-tetralone (4.93g) was refluxed for 30 minutes. The reaction mixture was cooled to 0°C, and to the mixture was gradually added 3N hydrochloric acid (80ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in THF (30ml), and to the mixture was added sodium boron hydride (494mg) at 0°C and then was dropwise added methanol (3ml) for 30 minutes. The reaction mixture was stirred at 0°C for 4 hours, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in methanol (20ml), and to the mixture was added 1N sodium hydroxide (20ml). The mixture was refluxed for 4 hours, cooled, acidified with concentrated

hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in Diglyme (20ml), and to the mixture was added concentrated hydrochloric acid (4ml). The mixture was stirred at 100°C for 2 hours, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, and concentrated under reduced pressure. The residue was dissolved in 0.5N sodium hydroxide (400ml), and the mixture was washed with diethylether. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-(4-methyl-phenyl)-3,4-dihydronaphthalene-2-carboxylic acid (1.96g) as pale brown crystals. mp 230-231°C

Elemental Analysis for $C_{18}H_{16}O_2$

Calcd: C, 81.79; H, 6.10.

Found: C, 81.62; H, 6.11.

IR (KBr) cm^{-1} : 3023, 2908, 1697, 1682, 1626, 1431, 1300, 928, 810

1H NMR (200MHz, $CDCl_3$) δ : 2.40 (3H, s), 2.61-2.71 (2H, m), 2.89-2.98 (2H, m), 7.22-7.28 (3H, m), 7.45-7.51 (4H, m), 7.73 (1H, s).

30 Reference Example 26

A mixture of sodium methoxide (15.5g), dimethyl carbonate (91ml) and 7-(4-fluorophenyl)-1-tetralone (13.8g) was refluxed for 30 minutes. The reaction mixture was cooled to 0°C, and to the mixture was gradually added 3N hydrochloric acid (200ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated

- sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in THF (90ml), and to the mixture was added sodium boron hydride (1.36g) at 0°C and then was
- 5 dropwise added methanol (9ml) for 30 minutes. The reaction mixture was stirred at 0°C for 4 hours, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, and concentrated under reduced
- 10 pressure. The residue was dissolved in methanol (80ml), and to the mixture was added 1N sodium hydroxide (100ml). The mixture was refluxed for 4 hours and cooled to room temperature. The mixture was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The
- 15 organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in Diglyme (50ml), and to the mixture was added concentrated hydrochloric acid (10ml). The mixture was
- 20 stirred at 100°C for 2 hours, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, and concentrated under reduced pressure. The
- 25 residue was dissolved in 0.5N sodium hydroxide (400ml), and the mixture was washed with diethylether. The aqueous layer was separated, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under
- 30 reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-(4-fluorophenyl)-3,4-dihydronaphthalene-2-carboxylic acid (6.01g) as pale brown crystals.
- mp 213-214°C
- 35 Elemental Analysis for $C_{17}H_{13}O_2F$
Calcd: C, 76.11; H, 4.88.

Found: C, 76.02; H, 4.97.

IR (KBr) cm^{-1} : 2953, 1695, 1518, 1431, 1300, 1281, 1246, 930, 824

^1H NMR (200MHz, CDCl_3) δ : 2.61-2.72 (2H, m), 2.90-2.99 (2H, m), 7.08-7.19 (2H, m), 7.23-7.29 (1H, m), 7.41-7.58 (4H, m), 7.72 (1H, s).

Reference Example 27

To a mixture of N-[4-(hydroxymethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (566mg), lithium chloride (135mg), triethylamine (446 μl) and dichloromethane (50ml) was added methanesulfonyl chloride (172 μl), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added dilute hydrochloric acid. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give N-[4-(chloromethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (494mg) as colorless crystals.

mp 176-177°C

Elemental Analysis for $\text{C}_{24}\text{H}_{20}\text{NOCl}$

Calcd: C, 77.10; H, 5.39; N, 3.75.

Found: C, 76.95; H, 5.47; N, 3.82.

IR (KBr) cm^{-1} : 3327, 1649, 1618, 1527, 1412, 1317, 831, 764, 700

^1H NMR (200MHz, $\text{DMSO}-d_6$) δ : 2.55-2.68 (2H, m), 2.85-2.95 (2H, m), 4.74 (2H, s), 7.30-7.80 (13H, m), 10.05 (1H, s).

Reference Example 28

A mixture of 4-nitrobenzylalcohol (10.0g), tert-butyl-dimethylsilyl chloride (11.8g), imidazole (11.2g) and DMF (50ml) was stirred at room temperature for 1.5 hours. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced

pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane= 1/7) to give tert-butyl dimethyl-4-nitrobenzyloxysilane (17.5g) as pale yellow oil.

- 5 ¹H NMR (200MHz, CDCl₃) δ: 0.13 (6H, s), 0.96 (9H, s), 4.83 (2H, s), 7.48 (2H, d, J=8.6Hz), 8.20 (2H, d, J=8.6Hz).
Reference Example 29

- 10 In ethanol (80ml) was dissolved tert-butyl dimethyl-4-nitrobenzyloxysilane (16.5g), and to the mixture was added dried 5% palladium on carbon (0.83g). Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 7.5 hours. The palladium was filtered off, and the filtrate was concentrated. The residue was separated and purified with column
15 chromatography (ethyl acetate/hexane=1/4) to give 4-aminobenzyloxy-tert-butyl dimethylsilane (13.8g) as colorless oil.

- IR (neat) cm⁻¹: 3359, 2954, 2856, 1626, 1518, 1471, 1375, 1257, 1072, 837, 777
20 ¹H NMR (200MHz, CDCl₃) δ: 0.07 (6H, s), 0.92 (9H, s), 3.50-3.70 (2H, br), 4.62 (2H, s), 6.65 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).
Reference Example 30

- 25 In THF (60ml) was dissolved 7-(4-methylphenyl)-3,4-dihydro-naphthalene-2-carboxylic acid (4.02g). To the solution were added oxalyl chloride (1.99ml) and a drop of DMF, and the mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (30ml), and to the mixture was dropwise
30 added a solution of 4-amino-benzyloxy-tert-butyl dimethylsilane (3.97g) and triethylamine (2.56ml) in THF (30ml) at room temperature. The reaction mixture was stirred at room temperature for 19 hours. To the mixture was added water (300ml), and the mixture was extracted with ethyl acetate.
35 The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and

concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene/hexane=1/5/5). The resulting oil was dissolved in acetone (60ml), and to the mixture was added
5 6N hydrochloric acid (2ml). The mixture was stirred at room temperature for 30 minutes. To the reaction mixture were added 0.5% sodium hydroxide (500ml) and diisopropylether (200ml), and the mixture was stirred at room temperature for 5 minutes. The resulting precipitate was filtered and
10 recrystallized from acetone-diisopropylether to give N-[4-(hydroxy-methyl)phenyl]-7-(4-methylphenyl)-3,4-dihydro-naphthalene-2-carboxamide (4.54g) as pale brown crystals.

mp 219-220°C

15 Elemental Analysis for $C_{25}H_{23}NO_2$

Calcd: C, 81.27; H, 6.27; N, 3.79.

Found: C, 81.23; H, 5.99; N, 3.80.

IR (KBr) cm^{-1} : 3315, 1647, 1618, 1597, 1531, 1414, 1321, 810

1H NMR (200MHz, DMSO- d_6) δ : 2.35 (3H, s), 2.55-2.65 (2H, m),
20 2.83-2.93 (2H, m), 4.46 (2H, d, $J=5.6Hz$), 5.13 (1H, t, $J=5.6Hz$), 7.23-7.33 (5H, m), 7.44-7.58 (5H, m), 7.69 (2H, d, $J=8.4Hz$), 9.93 (1H, s).

Reference Example 31

To a mixture of N-[4-(hydroxymethyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide
25 (2.20g), lithium chloride (505mg), triethylamine (1.67ml), DMAP [4-dimethylaminopyridine] (catalytic amount) and dichloromethane (200ml) was added methanesulfonyl chloride (645 μ l), and the mixture was stirred at room temperature
30 for 42 hours and concentrated under reduced pressure. To the residue was added 0.5N hydrochloric acid (200ml), and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was
35 recrystallized from ethyl acetate-hexane to give N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-

dihydronaphthalene-2-carboxamide (973mg) as colorless crystals.

mp 178-179°C

Elemental Analysis for $C_{15}H_{11}NO$

5 Calcd: C, 77.41; H, 5.72; N, 3.61.

Found: C, 77.34; H, 5.89; N, 3.65.

IR (KBr) cm^{-1} : 3332, 1651, 1620, 1529, 1412, 1319, 812

1H NMR (200MHz, DMSO- d_6) δ : 2.35 (3H, s), 2.55-2.68 (2H, m),

2.83-2.93 (2H, m), 4.74 (2H, s), 7.24-7.60 (10H, m), 7.76
10 (2H, d, $J=8.6Hz$), 10.04 (1H, s).

Reference Example 32

Under argon atmosphere, 6-methoxy-1-indanone (10.0g) was dissolved in xylene (100ml), and to the mixture was added aluminum chloride (16.4g). The mixture was refluxed for 2
15 hours and then cooled to room temperature. To the mixture was added 3N hydrochloric acid (100ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced
20 pressure. The residue was separated and purified with column chromatography (ethyl acetate) to give 6-hydroxy-1-indanone (7.36g) as pale brown crystals.

1H NMR (200MHz, $CDCl_3$) δ : 2.67-2.76 (2H, m), 3.02-3.11 (2H, m), 5.61 (1H, s), 7.10-7.21 (2H, m), 7.36 (1H, d, $J=8.0Hz$).

25 Reference Example 33

Under argon atmosphere, 6-hydroxy-1-indanone (7.36g) and triethylamine (20.9ml) were dissolved in dichloromethane (120ml), and to the mixture was dropwise added trifluoromethanesulfonic acid anhydride (8.78ml) at 0°C.
30 The reaction mixture was stirred at 0°C for 1 hour, and to the mixture was added water (200ml). The organic layer was separated, washed with water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl
35 acetate/hexane=1/4) to give 6-(trifluoromethanesulfoxy)-1-indanone (11.5g) as brown oil.

¹H NMR (200MHz, CDCl₃) δ: 2.75-2.83 (2H, m), 3.17-3.24 (2H, m), 7.50 (1H, dd, J=2.4, 8.4Hz), 7.60 (1H, d, J=8.4Hz), 7.64 (1H, d, J=2.4Hz).

Reference Example 34

- 5 Under argon atmosphere, a mixture of 6-(trifluoromethanesulfoxy)-1-indanone (11.5g), 4-methylphenyl borate (6.69g), potassium carbonate (11.3g), toluene (400ml), ethanol (40ml) and water (40ml) was stirred at room temperature for 30 minutes, and to the mixture was added
10 tetrakis(triphenylphosphine)palladium (1.42g). The mixture was refluxed for 17 hours and cooled to room temperature. The organic layer was separated, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column
15 chromatography (ethyl acetate/toluene=1/10) and recrystallized from ethyl acetate-hexane to give 6-(4-methylphenyl)-1-indanone (5.20g) as pale brown crystals. mp 121-122°C

Elemental Analysis for C₁₆H₁₄O

20 Calcd: C, 86.45; H, 6.35.

Found: C, 86.46; H, 6.23.

IR (KBr) cm⁻¹: 1703, 1614, 1483, 1448, 1404, 1304, 814

¹H NMR (200MHz, CDCl₃) δ: 2.40 (3H, s), 2.70-2.79 (2H, m), 3.13-3.22 (2H, m), 7.23-7.29 (2H, m), 7.48-7.57 (3H, m),
25 7.83 (1H, dd, J=1.8, 8.0Hz), 7.96 (1H, s).

Reference Example 35

- A solution of 6-(4-methylphenyl)-1-indanone (4.97g) in THF (33ml) was dropwise added to a refluxed mixture of
60% sodium hydride (3.26g), potassium hydride (catalytic amount), dimethyl carbonate (6.65ml) and THF (100ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled to 0°C, and to the mixture was gradually added
2N hydrochloric acid (150ml). The mixture was extracted with ethyl acetate, and the organic layer was washed with
35 saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure.

The residue was separated and purified with column chromatography (ethyl acetate/toluene=1/3) to give a brown solid. The solid was dissolved in dichloromethane (100ml), and to the mixture was added sodium boron hydride (391mg) at 0°C and then was dropwise added methanol (10ml). The reaction mixture was stirred at 0°C for 1.5 hours, and to the mixture was added water (500ml). The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in methanol (30ml), and to the mixture was added 1N sodium hydroxide (40ml). The mixture was refluxed for 2 hours and cooled to room temperature. To the mixture was added water, and the mixture was washed with diethylether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in Diglyme (30ml), and to the mixture was added concentrated hydrochloric acid (6ml). The mixture was stirred at 100°C for 2 hours, and to the solution were added 0.5% sodium hydrogen carbonate solution (500ml) and hexane (500ml). The resulting precipitate was filtered to give 5-(4-methylphenyl)-indene-2-carboxylic acid (2.72g) as brown crystals.

mp 226-229°C (decomp.)

Elemental Analysis for $C_{17}H_{14}O_2 \cdot 0.1H_2O$

Calcd: C, 80.99; H, 5.68.

Found: C, 80.92; H, 5.55.

IR (KBr) cm^{-1} : 2999, 1670, 1572, 1259, 808

1H NMR (200MHz, DMSO- d_6) δ : 2.35 (3H, s), 3.63-3.70 (2H, m), 7.28 (2H, d, $J=8.0Hz$), 7.53-7.73 (5H, m), 7.83 (1H, d, $J=6.0Hz$).

Reference Example 36

A mixture of hexamethyleneimine (15.0g), ethyl iodide

(14.5ml), potassium carbonate (31.3g) and ethanol (300ml) was refluxed for 6 hours and concentrated under reduced pressure. To the residue was added diethylether, and insoluble material was filtered off. The filtrate was under
5 reduced pressure to give 1-ethylperhydroazepine (4.56g) as colorless oil.

bp 73-76°C/70mmHg

IR (neat) cm^{-1} : 2927, 1452, 1352, 1190, 1140, 1093

^1H NMR (200MHz, CDCl_3) δ : 1.05 (3H, t, $J=7.2\text{Hz}$), 1.55-1.72
10 (8H, m), 2.47-2.65 (6H, m).

Reference Example 37

A mixture of hexamethyleneimine (15.0g), 1-propyl iodide (29.5ml), potassium carbonate (31.3g) and ethanol (300ml) was refluxed for 42 hours and concentrated under
15 reduced pressure. To the residue was added diethylether, and insoluble material was filtered off. The filtrate was under reduced pressure to give 1-propylperhydroazepine (2.50g) as colorless oil.

bp 70-74°C/50mmHg

20 IR (neat) cm^{-1} : 2926, 1749, 1458, 1375, 1259, 1184, 1138, 1082

^1H NMR (200MHz, CDCl_3) δ : 0.87 (3H, t, $J=7.5\text{Hz}$), 1.40-1.80 (10H, m), 2.36-2.46 (2H, m), 2.55-2.67 (4H, m).

Reference Example 38

25 A mixture of heptamethyleneimine (10.0g), ethyl iodide (8.48ml), potassium carbonate (18.3g) and ethanol (200ml) was refluxed for 13 hours and concentrated under reduced pressure. To the residue was added diethylether, and insoluble material was filtered off. The filtrate was under
30 reduced pressure to give 1-ethylperhydroazocine (2.29g) as colorless oil.

bp 76-78°C/40mmHg

IR (neat) cm^{-1} : 2920, 1475, 1446, 1371, 1252, 1225, 1161, 1093

35 ^1H NMR (200MHz, CDCl_3) δ : 1.03 (3H, t, $J=6.9\text{Hz}$), 1.48-1.72 (10H, m), 2.42-2.60 (6H, m).

Reference Example 39

Under argon atmosphere, a mixture of methyl (E)-3-(trifluoromethanesulfoxy)cinnamate (9.00g), 4-methylphenyl borate (4.73g), potassium carbonate (8.02g), toluene (300ml), ethanol (30ml) and water (30ml) was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (1.01g), and the mixture was refluxed for 24 hours. The reaction mixture was cooled to room temperature, and the organic layer was separated, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene/hexane=1/5/5) to give colorless oil, which was dissolved in methanol (50ml). To the mixture was added 1N sodium hydroxide (50ml), and the mixture was refluxed for 1 hour. The reaction mixture was cooled to room temperature, acidified with concentrated hydro-chloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-3-(4-methylphenyl)cinnamic acid (5.15g) as colorless crystals. mp 192-194°C

25 Elemental Analysis for $C_{16}H_{14}O_2 \cdot 0.1H_2O$

Calcd: C, 80.04; H, 5.96.

Found: C, 80.13; H, 5.94.

IR (KBr) cm^{-1} : 2922, 1687, 1628, 1435, 1321, 1282, 1225, 798

1H NMR (200MHz, $CDCl_3$) δ : 2.41 (3H, s), 6.52 (1H, d, J=16.0Hz), 7.23-7.30 (2H, m), 7.40-7.53 (4H, m), 7.56-7.65 (1H, m), 7.73 (1H, s), 7.85 (1H, d, J=16.0Hz).

Reference Example 40

In THF (50ml) was dissolved (E)-3-(4-methylphenyl)-cinnamic acid (5.00g), and to the solution were added oxalyl chloride (2.38ml) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced

pressure. The residue was dissolved in THF (50ml), and to the mixture were added 4-aminobenzyloxy-tert-butyl-dimethylsilane (5.48g) and triethylamine (3.53ml) at room temperature. The reaction mixture was stirred at room temperature for 3 hours, and to the mixture was added water (200ml). The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene/hexane=1/5/5) to give oil, which was dissolved in acetone (50ml). To the mixture was added 6N hydrochloric acid (1ml), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture were added 0.5% sodium hydroxide (500ml) and diisopropylether (200ml), and the mixture was stirred at room temperature for 5 minutes. The resulting precipitate was filtered and recrystallized from acetone-diisopropylether to give (E)-N-[4-(hydroxymethyl)-phenyl]-3-(4-methylphenyl)-cinnamamide (6.18g) as pale yellow crystals.
mp 220-223°C

Elemental Analysis for $C_{23}H_{21}NO_2$

Calcd: C, 80.44; H, 6.16; N, 4.08.

Found: C, 80.12; H, 6.15; N, 4.00.

IR (KBr) cm^{-1} : 3294, 1662, 1624, 1603, 1541, 1516, 1414, 1346, 1250, 1184, 999, 787

1H NMR (200MHz, DMSO- d_6) δ : 2.36 (3H, s), 4.46 (2H, s), 6.93 (1H, d, J=15.4Hz), 7.22-7.33 (4H, m), 7.46-7.71 (8H, m), 7.89 (1H, s), 10.18 (1H, s).

Reference Example 41

To a mixture of (E)-N-[4-(hydroxymethyl)phenyl]-3-(4-methylphenyl)cinnamamide (3.00g), lithium chloride (741mg), triethylamine (3.06ml), DMAP(catalytic amount) and dichloro-methane (300ml) was added methanesulfonyl chloride (1.15ml), and the mixture was stirred at room temperature for 13 hours. To the reaction mixture was added

4N hydrochloric acid ethyl acetate solution (3.3ml), and the mixture was purified with column chromatography (ethyl acetate) and recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-(chloromethyl)phenyl]-3-(4-methylphenyl)cinnamamide (2.00g) as colorless crystals.

mp 178-180°C

Elemental Analysis for $C_{23}H_{20}NOCl \cdot 0.1H_2O$

Calcd: C, 75.96; H, 5.60; N, 3.85.

10 Found: C, 75.93; H, 5.50; N, 3.88.

IR (KBr) cm^{-1} : 3344, 3045, 1664, 1628, 1531, 1412, 1338, 1248, 1176, 968, 793, 658

1H NMR (200MHz, $CDCl_3$) δ : 2.41 (3H, s), 4.58 (2H, s), 6.61 (1H, d, $J=15.6Hz$), 7.25-7.31 (2H, m), 7.33-7.53 (7H, m),

15 7.55-7.67 (3H, m), 7.74 (1H, s), 7.83 (1H, d, $J=15.6Hz$).

Reference Example 42

To a solution cooled at -78°C of 2-bromopyridine (10.0g) in diethylether (200ml) was dropwise added 1.6M butyllithium hexane solution (39.6ml) for 10 minutes. The mixture was stirred at -78°C for 1 hour, and to the mixture was dropwise added a solution of 4-nitrobenzaldehyde in THF (50ml). The reaction mixture was stirred at -78°C for 3 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/toluene=1/2) and re-crystallized from diisopropylether to give (4-nitro-phenyl)-(2-pyridyl)methanol (4.50g) as orange crystals.

mp 114-115°C

Elemental Analysis for $C_{12}H_{10}N_2O_3$

Calcd: C, 62.61; H, 4.38; N, 12.17.

Found: C, 62.61; H, 4.27; N, 12.16.

35 IR (KBr) cm^{-1} : 3113, 2852, 1595, 1506, 1437, 1336, 1267, 1068, 1047, 1007, 847, 814, 777, 756, 743, 706

¹H NMR (200MHz, CDCl₃) δ : 5.44 (1H, br s), 5.86 (1H, s), 7.14-7.29 (2H, m), 7.55-7.73 (3H, m), 8.20 (2H, d, J=8.8Hz), 8.59 (1H, d, J=5.0Hz).

Reference Example 43

5 In ethanol (50ml) was dissolved (4-nitrophenyl)-(2-pyridyl)methanol (2.30g), and to the mixture was added dried 10% palladium on carbon (0.12g). Under hydrogen atmosphere, the mixture was stirred at room temperature under atmospheric pressure for 19 hours. The palladium was
10 filtered off, and the filtrate was concentrated. The residue was recrystallized from ethyl acetate-hexane to give (4-aminophenyl)(2-pyridyl)methanol (1.90g) as pale yellow crystals.

mp 139-140°C

15 Elemental Analysis for C₁₂H₁₂N₂O

Calcd: C, 71.98; H, 6.04; N, 13.99.

Found: C, 71.76; H, 6.01; N, 13.82.

IR (KBr) cm⁻¹: 3292, 1612, 1589, 1512, 1473, 1439, 1263, 1055, 816, 752, 569

20 ¹H NMR (200MHz, CDCl₃) δ : 3.65 (2H, br s), 5.14 (1H, br s), 5.65 (1H, s), 6.65 (2H, d, J=8.8Hz), 7.10-7.22 (4H, m), 7.61 (1H, dt, J=1.8, 7.6Hz) 8.55 (1H, d, J=4.8Hz).

Reference Example 44

Under argon atmosphere, ethyl 3-hydroxycinnamate (mp
25 88-89°C; 20.0g) and triethylamine (34.5ml) were dissolved in dichloromethane (200ml), and to the mixture was dropwise added trifluoromethanesulfonic acid anhydride (31.6g) at -5°C for 40 minutes. The reaction mixture was stirred at -5°C to 0°C for 20 minutes, and to the mixture was added water
30 (200ml). The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure.

The residue was separated and purified with column chromatography (ethyl acetate/hexane=1/4) and crystallized
35 from hexane to give ethyl 3-(trifluoro-methane-sulfoxy)cinnamate (33.5g).

mp 52-53°C

¹H NMR (200MHz, CDCl₃) δ : 3.83 (3H, s), 6.48 (1H, d, J=16.0Hz), 7.30 (1H, m), 7.41 (1H, t, J=1.6Hz), 7.51 (2H, m), 7.67 (1H, d, J=16.0Hz).

5 Reference Example 45

Under argon atmosphere, a mixture of ethyl 3-(trifluoromethanesulfoxy)cinnamate (3.10g), 4-methylphenyl borate (1.63g), potassium carbonate (2.76g), toluene (100ml), ethanol (10ml) and water (10ml) was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.46g), and the mixture was refluxed for 18 hours. The reaction mixture was cooled to room temperature. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1/6) to give ethyl 3-(4-methylphenyl)-cinnamate (2.21g) as colorless oil. The oil (2.20g) was dissolved in tetrahydrofuran (20ml). To the mixture was added 2N sodium hydroxide (8.7ml), and the mixture was stirred at 50°C for 2 hours. The reaction mixture was cooled, acidified with potassium hydrogen sulfate and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was washed with isopropylether to give 3-(4-methylphenyl)-cinnamic acid (1.54g) as colorless crystals.

mp 186-187°C

30 ¹H NMR (200MHz, CDCl₃) δ : 2.41 (3H, s), 6.53 (1H, d, J=16.0Hz), 7.28 (2H, d, J=7.4Hz), 7.46-7.52 (4H, m), 7.50 (1H, s), 7.63 (1H, m), 7.86 (1H, d, J=16.0Hz).

Reference Example 46

Under argon atmosphere, a mixture of ethyl 3-(trifluoromethanesulfoxy)cinnamate (3.10g), 2-methylphenyl borate (mp 165-166°C; 1.63g), potassium carbonate

(2.76g), toluene (100ml), ethanol (10ml) and water (10ml) was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl-phosphine)palladium (0.46g), and the mixture was refluxed for 18 hours. The reaction mixture was cooled to room temperature, and the organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane= 1/6) to give ethyl 3-(4-methylphenyl)-cinnamate (2.51g) as pale yellow oil. The oil (2.50g) was dissolved in tetrahydrofuran (20ml). To the mixture was added 2N sodium hydroxide (10.0ml), and the mixture was stirred at 50°C for 2 hours. The reaction mixture was cooled, acidified with potassium hydrogen sulfate and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was washed with isopropylether to give 3-(2-methylphenyl)cinnamic acid (1.96g) as colorless crystals. mp 124-125°C

¹H NMR (200MHz, CDCl₃) δ : 2.27 (3H, s), 6.49 (1H, d, J=16.0Hz), 7.23-7.30 (4H, m), 7.36-7.57 (4H, m), d, J=7.4Hz), 7.84 (1H, d, J=16.0Hz).

25 Reference Example 47

Under argon atmosphere, a mixture of ethyl 3-(trifluoro-methanesulfoxy)cinnamate (3.10g), 2,5-dimethylphenyl borate (mp 184-186°C; 1.80g), potassium carbonate (2.76g), toluene (100ml), ethanol (10ml) and water (10ml) was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)-palladium (0.46g), and the mixture was refluxed for 27 hours. The reaction mixture was cooled to room temperature, and the organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The

residue was separated and purified with column chromatography (ethyl acetate/hexane= 1/6) to give ethyl 3-(2,5-dimethylphenyl)cinnamate (2.66g) as pale yellow oil. The oil (2.50g) was dissolved in tetrahydrofuran (20ml), and to the mixture was added 2N sodium hydroxide (10.0ml). The mixture was stirred at 50°C for 2 hours, cooled, acidified with potassium hydrogen sulfate and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was washed with isopropylether to give 3-(2,5-dimethylphenyl)cinnamic acid (1.96g) as colorless crystals.

mp 156-157°C

¹H NMR (200MHz, CDCl₃) δ : 2.23 (3H, s), 2.60 (3H, s), 6.49 (1H, d, J=16.0Hz), 7.06 (1H, s), 7.14 (2H, ABq, J=7.8Hz), 7.35-7.55 (4H, m), 7.36-7.57 (4H, m), 7.84 (1H, d, J=16.0Hz).

Reference Example 48

Under argon atmosphere, a mixture of ethyl 3-(trifluoromethanesulfoxy)cinnamate (3.10g), 3-nitrophenyl borate (2.00g), potassium carbonate (2.76g), toluene (100ml), ethanol (10ml) and water (10ml) was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.46g), and the mixture was refluxed for 24 hours. The reaction mixture was cooled to room temperature. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1/6) to give ethyl 3-(3-nitrophenyl)-cinnamate (2.40g) as pale yellow crystals. The crystals (2.40g) were dissolved in tetrahydrofuran (20ml), and to the mixture was added 2N sodium hydroxide (8.5ml). The mixture was stirred at 50°C for 2 hours, cooled, acidified with potassium hydrogen sulfate and extracted with ethyl acetate. The organic layer

was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was washed with isopropylether to give 3-(3-nitrophenyl)cinnamic acid (1.88g) as pale yellow crystals.

mp 247-248°C

¹H NMR (200MHz, DMSO-d₆) δ: 6.59 (1H, d, J=16.0Hz), 7.51-7.76 (4H, m), 7.70 (1H, d, J=16.0Hz), 7.96 (1H, d, J=9.0Hz), 8.09 (1H, m), 8.22 (1H, m), 8.49 (1H, d, J=1.8Hz).

10 Working Example 1 (Production of Compound 1)

In THF (5ml) was dissolved 7-cyclohexyl-3,4-dihydronaphthalene-2-carboxylic acid (200mg), and to the solution were added oxalyl chloride (82μl) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (5ml), and to the solution were added 1-(4-aminobenzyl)piperidine (164mg) and triethylamine (484μl) at room temperature. The reaction mixture was stirred at room temperature for 3 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-cyclohexyl-N-[4-(piperidinomethyl)-phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 1) (223mg) as colorless crystals.

mp 180-181°C

Elemental Analysis for C₂₂H₂₆N₂O₂

30 Calcd: C, 81.27; H, 8.47; N, 6.54.

Found: C, 81.03; H, 8.42; N, 6.53.

IR (KBr) cm⁻¹: 3430, 2931, 1645, 1597, 1514, 1412, 1317, 824

¹H NMR (200MHz, CDCl₃) δ: 1.20-1.90 (16H, m), 2.30-2.57 (5H, m), 2.60-2.72 (2H, m), 2.85-2.97 (2H, m), 3.46 (2H, s),

35 7.05-7.15 (3H, m), 7.25-7.34 (3H, m), 7.50-7.60 (3H, m).

Working Example 2 (Production of Compound 2)

In DMF (2ml) was dissolved 7-cyclohexyl-N-[4-(piperidinomethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (120mg), and to the mixture was added methyl iodide (45 μ l). The mixture was stirred at room temperature for 24 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 1-[4-(7-cyclohexyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]-1-methylpiperidinium iodide (Compound 2) (148mg) as colorless crystals.

mp 188-191°C

Elemental Analysis for $C_{30}H_{39}N_2OI$

Calcd: C, 63.15; H, 6.89; N, 4.91; I, 22.24.

Found: C, 63.03; H, 6.93; N, 5.03; I, 22.22.

IR (KBr) cm^{-1} : 3430, 2929, 1649, 1599, 1520, 1417, 1321, 1248

1H NMR (200MHz, DMSO- d_6) δ : 1.20-1.90 (16H, m), 2.40-2.65 (3H, m), 2.75-2.95 (5H, m), 3.20-3.45 (4H, m), 4.53 (2H, s), 7.14 (3H, s), 7.38 (1H, s), 7.49 (2H, d, J=8.6Hz), 7.88 (2H, d, J=8.6Hz), 10.12 (1H, s).

Working Example 3 (Production of Compound 3)

In THF (3ml) was dissolved 7-cyclohexyl-3,4-dihydronaphthalene-2-carboxylic acid (100mg), and to the solution were added oxalyl chloride (41 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (3ml), and to the solution were added p-(4-aminobenzyl)-N,N'-diethyl-phosphondiamide (104mg) and triethylamine (60 μ l) at room temperature. The reaction mixture was stirred at room temperature for 72 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/methanol =10/1) and was recrystallized from diisopropylether to give 7-cyclohexyl-N-[4-[bis(ethylamino)phosphorylmethyl]-

phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 3)
(140mg) as colorless crystals.

mp 163-165°C

Elemental Analysis for $C_{22}H_{18}N_2O_2$

5 Calcd: C, 70.12; H, 7.99; N, 8.76.

Found: C, 70.01; H, 7.99; N, 8.93.

IR (KBr) cm^{-1} : 3250, 2926, 1645, 1599, 1514, 1414, 1321, 1250,
1182, 1126

1H NMR (200MHz, $CDCl_3$) δ : 1.10 (6H, t, $J=7.1Hz$), 1.20-1.90
10 (10H, m), 1.95-2.20 (2H, m), 2.40-2.57 (1H, m), 2.60-2.72
(2H, m), 2.80-3.05 (7H, m), 3.12 (1H, s), 7.05-7.15 (3H,
m), 7.22-7.32 (3H, m), 7.59 (2H, d, $J=8.2Hz$), 7.83 (1H, s).

Working Example 4 (Production of Compound 4)

In THF (20ml) was dissolved 7-phenyl-3,4-dihydro-
15 naphthalene-2-carboxylic acid (1.00g), and to the solution
were added oxalyl chloride ($523\mu l$) and a drop of DMF. The
mixture was added at room temperature for 1 hour and
concentrated under reduced pressure. The residue was
dissolved in THF (20ml), and to the solution were added
20 1-(4-aminobenzyl)piperidine (837mg) and triethylamine (673
 μl) at room temperature. The reaction mixture was stirred
at room temperature for 2 hours, and to the mixture was added
water (150ml). The mixture was extracted with ethyl acetate.
The organic layer was washed with saturated sodium chloride
25 solution, dried with anhydrous sodium sulfate, and
concentrated under reduced pressure. The residue was
recrystallized from ethyl acetate-diisopropylether to give
7-phenyl-N-[4-(piperidinomethyl)phenyl]-3,4-dihydro-
naphthalene-2-carboxamide (Compound 4) (1.15g) as pale
30 brown crystals.

mp 163-164°C

Elemental Analysis for $C_{29}H_{30}N_2O \cdot 0.1H_2O$

Calcd: C, 82.08; H, 7.17; N, 6.60.

Found: C, 81.94; H, 7.22; N, 6.49.

35 IR (KBr) cm^{-1} : 3336, 2935, 1651, 1527, 1412, 1317, 762, 698

1H NMR (200MHz, $CDCl_3$) δ : 1.35-1.70 (6H, m), 2.30-2.45 (4H,

m), 2.65-2.80 (2H, m), 2.92-3.04 (2H, m), 3.46 (2H, s), 7.23-7.62 (14H, m).

Working Example 5 (Production of Compound 5)

In DMF (3ml) was dissolved 7-phenyl-N-[4-(piperidino-
5 methyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide
(240mg), and to the mixture was added methyl iodide (106
 μ l). The mixture was stirred at room temperature for 60
hours and concentrated under reduced pressure. The residue
was recrystallized from ethyl acetate to give 1-methyl-
10 1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-
carboxamido)benzyl]piperidinium iodide (Compound 5)
(247mg) as colorless crystals.
mp 183-186°C

Elemental Analysis for $C_{20}H_{23}N_2OI$

15 Calcd: C, 63.83; H, 5.89; N, 4.96.

Found: C, 63.54; H, 5.82; N, 5.05.

IR (KBr) cm^{-1} : 3450, 1649, 1599, 1520, 1417, 1319

1H NMR (200MHz, DMSO- d_6) δ : 1.40-2.00 (6H, m), 2.55-2.70 (2H,
m), 2.80-3.00 (5H, m), 3.20-3.45 (4H, m), 4.53 (2H, s),
20 7.30-7.70 (11H, m), 7.89 (2H, d, $J=8.6Hz$), 10.18 (1H, s).

Working Example 6 (Production of Compound 6)

In THF (10ml) was dissolved 7-phenyl-3,4-dihydro-
naphthalene-2-carboxylic acid (500mg), and to the solution
were added oxalyl chloride (262 μ l) and a drop of DMF. The
25 mixture was stirred at room temperature for 1 hour and
concentrated under reduced pressure. The residue was
dissolved in THF (10ml), and to the solution were added
4-aminobenzyl dimethylamine (330mg) and triethylamine (337
 μ l) at room temperature. The reaction mixture was stirred
30 at room temperature for 3 hours, and to the mixture was added
water (100ml). The mixture was extracted with ethyl acetate.
The organic layer was washed with saturated sodium chloride
solution, dried with anhydrous sodium sulfate, and
concentrated under reduced pressure. The residue was
35 separated and purified with column chromatography (ethyl
acetate/triethylamine=20/1) and recrystallized from ethyl

acetate-hexane to give N-[4-(dimethylaminomethyl)-phenyl]-7-phenyl-3,4-dihydro-naphthalene-2-carboxamide (Compound 6) (131mg) as colorless crystals.

mp 182-184°C

5 Elemental Analysis for $C_{26}H_{26}N_2O \cdot 0.2H_2O$

Calcd: C, 80.88; H, 6.89; N, 7.26.

Found: C, 81.00; H, 6.90; N, 7.19.

IR (KBr) cm^{-1} : 3328, 1649, 1529, 1410, 1317, 762, 698

1H NMR (200MHz, $CDCl_3$) δ : 2.24 (6H, s), 2.65-2.80 (2H, m),

10 2.94-3.03 (2H, m), 3.41 (2H, s), 7.25-7.63 (14H, m).

Working Example 7 (Production of Compound 7)

In THF (10ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (500mg), and to the solution were added oxalyl chloride (262 μ l) and a drop of DMF. The
15 mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the solution were added 1-(4-aminobenzyl)pyrrolidine (388mg) and triethylamine (337 μ l) at room temperature. The reaction mixture was
20 stirred at room temperature for 3 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The
25 residue was separated and purified with column chromatography (ethyl acetate/ triethylamine=20/1) and recrystallized from ethyl acetate-diisopropylether to give 7-phenyl-N-[4-(1-pyrrolidinylmethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 7) (107mg) as
30 colorless crystals.

mp 186-187°C

Elemental Analysis for $C_{26}H_{26}N_2O \cdot 0.1H_2O$

Calcd: C, 81.96; H, 6.93; N, 6.83.

Found: C, 81.78; H, 6.84; N, 6.89.

35 IR (KBr) cm^{-1} : 3329, 2962, 1649, 1529, 1410, 1319, 762, 698

1H NMR (200MHz, $CDCl_3$) δ : 1.75-1.85 (4H, m), 2.45-2.55 (4H,

m), 2.65-2.80 (2H, m), 2.90-3.05 (2H, m), 3.60 (2H, s), 7.25-7.60 (14H, m).

Working Example 8 (Production of Compound 8)

In THF (10ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (500mg), and to the solution were added oxalyl chloride (262 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the solution were added 1-(4-aminobenzyl)morpholine (423mg) and triethylamine (337 μ l) at room temperature. The reaction mixture was stirred at room temperature for 2 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate.

The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate) and recrystallized from ethyl acetate-hexane to give N-[4-(morpholinomethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (659mg) as colorless crystals.

mp 186-187°C

Elemental Analysis for $C_{28}H_{28}N_2O_2$

Calcd: C, 79.22; H, 6.65; N, 6.60.

Found: C, 78.89; H, 6.50; N, 6.66.

IR (KBr) cm^{-1} : 3450, 1651, 1620, 1597, 1527, 1412, 1319, 1113, 764, 700

^1H NMR (200MHz, CDCl_3) δ : 2.38-2.47 (4H, m), 2.66-2.78 (2H, m), 2.92-3.03 (2H, m), 3.48 (2H, s), 3.67-3.75 (4H, m),

7.25-7.60 (14H, m).

Working Example 9 (Production of Compound 9)

In THF (10ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (500mg), and to the solution were added oxalyl chloride (262 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was

dissolved in THF (10ml), and to the solution were added
1-[2-(4-aminophenyl)ethyl]piperidine (450mg) and
triethylamine (337 μ l) at room temperature. The reaction
mixture was stirred at room temperature for 1 hour, and to
5 the mixture was added water (100ml). The mixture was
extracted with ethyl acetate. The organic layer was washed
with saturated sodium chloride solution, dried with
anhydrous sodium sulfate, and concentrated under reduced
pressure. The residue was recrystallized from ethyl
10 acetate-diisopropylether to give 7-phenyl-N-[4-(2-
piperidinoethyl)phenyl]-3,4-dihydro-naphthalene-2-
carboxamide (Compound 9) (576mg) as pale brown crystals.
mp 157-159°C

Elemental Analysis for $C_{20}H_{22}N_2O$

15 Calcd: C, 82.53; H, 7.39; N, 6.42.

Found: C, 82.29; H, 7.24; N, 6.32.

IR (KBr) cm^{-1} : 3332, 2933, 1651, 1524, 1412, 1317, 1257, 1117,
762, 698

1H NMR (200MHz, $CDCl_3$) δ : 1.40-1.80 (6H, m), 2.40-2.60 (6H,
20 m), 2.65-2.85 (4H, m), 2.90-3.00 (2H, m), 7.15-7.60 (14H,
m).

Working Example 10 (Production of Compound 10)

In DMF (2ml) was dissolved N-[4-(dimethylamino-
methyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-
25 carboxamide (80mg), and to the mixture was added methyl
iodide (39 μ l). The mixture was stirred at room temperature
for 17 hours and concentrated under reduced pressure. The
residue was recrystallized from methanol-
ethyl acetate to give trimethyl[4-(7-phenyl-3,4-dihydro-
30 naphthalene-2-carboxamido)benzyl]ammonium iodide
(Compound 10) (92mg) as colorless crystals.
mp 190-192°C

Elemental Analysis for $C_{27}H_{29}N_2OI \cdot 0.5H_2O$

Calcd: C, 60.79; H, 5.67; N, 5.25.

35 Found: C, 60.81; H, 5.59; N, 5.30.

IR (KBr) cm^{-1} : 3450, 1662, 1595, 1520, 1483, 1416, 1319, 1250,

764, 700

¹H NMR (200MHz, CDCl₃) δ: 2.65-2.80 (2H, m), 2.80-2.95 (2H, m), 3.23 (9H, s), 4.98 (2H, s), 7.18 (1H, d, J=8.0Hz), 7.30-7.60 (9H, m), 7.69 (1H, s), 7.82-7.90 (2H, m), 8.71 (1H, s).

Working Example 11 (Production of Compound 11)

In DMF (2ml) was dissolved 7-phenyl-N-[4-(1-pyrrolidinylmethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (70mg), and to the mixture was added methyl iodide (32μl). The mixture was stirred at room temperature for 17 hours and concentrated under reduced pressure. The residue was recrystallized from methanol-ethyl acetate to give 1-methyl-1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]pyrrolidinium iodide (Compound 11) (78mg) as pale yellow crystals.
mp 156-160°C

Elemental Analysis for C₂₂H₂₁N₂OI · 1.0H₂O

Calcd: C, 61.27; H, 5.85; N, 4.93.

Found: C, 61.23; H, 5.89; N, 5.04.

IR (KBr) cm⁻¹: 3442, 1655, 1593, 1520, 1416, 1317, 1248, 766, 700

¹H NMR (200MHz, CDCl₃) δ: 2.05-2.40 (4H, m), 2.65-2.76 (2H, m), 2.82-2.95 (2H, m), 3.05 (3H, s), 3.43-3.57 (2H, m), 3.80-4.00 (2H, m), 4.98 (2H, s), 7.18 (1H, d, J=8.0Hz), 7.30-7.56 (9H, m), 7.70 (1H, s), 7.80-7.90 (2H, m), 8.74 (1H, s).

Working Example 12 (Production of Compound 12)

In DMF (4ml) was dissolved N-[4-(morpholinomethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (450mg), and to the mixture was added methyl iodide (198μl). The mixture was stirred at room temperature for 18 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 4-methyl-4-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]morpholinium iodide (Compound 12) (575mg) as pale yellow crystals.

mp 166-170°C

Elemental Analysis for $C_{29}H_{31}N_2O_2I \cdot 0.5H_2O$

Calcd: C, 60.53; H, 5.60; N, 4.87.

Found: C, 60.41; H, 5.61; N, 4.74.

5 IR (KBr) cm^{-1} : 3450, 1653, 1593, 1520, 1481, 1416, 1317, 1246, 1122, 887, 764, 698

1H NMR (200MHz, $CDCl_3$) δ : 2.60-2.75 (2H, m), 2.75-2.90 (2H, m), 3.22 (3H, s), 3.35-3.50 (2H, m), 3.55-3.75 (2H, m), 3.80-4.05 (4H, m), 5.13 (2H, s), 7.12 (1H, d, $J=7.6Hz$),
10 7.25-7.55 (9H, m), 7.71 (1H, s), 7.80-7.87 (2H, m), 8.95 (1H, s).

Working Example 13 (Production of Compound 13)

In DMF (4ml) was dissolved 7-phenyl-N-[4-(2-piperidinoethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (350mg), and to the mixture was added methyl
15 iodide (150 μ l). The mixture was stirred at room temperature for 14 hours and concentrated under reduced pressure. The residue was recrystallized from methanol-ethyl acetate to give 1-methyl-1-[2-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamide)phenyl]ethyl]-
20 piperidinium iodide (Compound 13) (410mg) as pale brown crystals.

mp 219-220°C

Elemental Analysis for $C_{31}H_{35}N_2OI \cdot 0.2H_2O$

25 Calcd: C, 63.96; H, 6.13; N, 4.81.

Found: C, 63.91; H, 6.06; N, 4.89.

IR (KBr) cm^{-1} : 2941, 1666, 1595, 1520, 1313, 1240, 1205, 837, 768, 702

1H NMR (200MHz, DMSO- d_6) δ : 1.45-1.90 (6H, m), 2.55-2.70 (2H, m), 2.80-3.17 (7H, m), 3.25-3.60 (6H, m), 7.25-7.80 (13H, m), 9.95 (1H, s).
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Working Example 14 (Production of Compound 14)

In THF (10ml) was dissolved 7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxylic acid (500mg), and to
35 the solution were added oxalyl chloride (248 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1

hour and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the solution were added 1-(4-aminobenzyl)piperidine (396mg) and triethylamine (318 μ l) at room temperature. The reaction mixture was stirred at room temperature for 14 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-(4-methylphenyl)-N-[4-(piperidinomethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 14) (616mg) as pale brown crystals.
mp 187-189°C

15 Elemental Analysis for $C_{26}H_{22}N_2O$

Calcd: C, 82.53; H, 7.39; N, 6.42.

Found: C, 82.26; H, 7.36; N, 6.37.

IR (KBr) cm^{-1} : 3310, 2931, 1643, 1599, 1527, 1412, 1315, 1255, 806

20 1H NMR (200MHz, $CDCl_3$) δ : 1.38-1.65 (6H, m), 2.32-2.42 (7H, m), 2.65-2.77 (2H, m), 2.92-3.02 (2H, m), 3.46 (2H, s), 7.20-7.34 (6H, m), 7.40-7.58 (7H, m).

Working Example 15 (Production of Compound 15)

In THF (10ml) was dissolved 7-(4-fluorophenyl)-3,4-dihydronaphthalene-2-carboxylic acid (500mg), and to the solution were added oxalyl chloride (243 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the solution were added 1-(4-aminobenzyl)piperidine (389mg) and triethylamine (313 μ l) at room temperature. The reaction mixture was stirred at room temperature for 14 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was

recrystallized from ethyl acetate-diisopropylether to give 7-(4-fluorophenyl)-N-[4-(piperidinomethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 15) (736mg) as pale yellow crystals.

5 mp 175-176°C

Elemental Analysis for $C_{25}H_{29}N_2OF \cdot 0.2H_2O$

Calcd: C, 78.42; H, 6.67; N, 6.31.

Found: C, 78.36; H, 6.68; N, 6.23.

IR (KBr) cm^{-1} : 3329, 2935, 1649, 1595, 1518, 1319, 1244, 824

10 1H NMR (200MHz, $CDCl_3$) δ : 1.35-1.65 (6H, m), 2.34-2.41 (4H, m), 2.67-2.77 (2H, m), 2.92-3.02 (2H, m), 3.46 (2H, s), 7.07-7.58 (13H, m).

Working Example 16 (Production of Compound 16)

In DMF (3ml) was dissolved 7-(4-methylphenyl)-N-[4-(piperidinomethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (400mg), and to the mixture was added methyl iodide (171 μ l). The mixture was stirred at room temperature for 18 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 1-methyl-1-[4-[7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]piperidinium iodide (Compound 16) (490mg) as colorless crystals.
20 mp 202-204°C

Elemental Analysis for $C_{31}H_{35}N_2OI \cdot 0.5H_2O$

25 Calcd: C, 63.37; H, 6.18; N, 4.77.

Found: C, 63.69; H, 5.98; N, 4.87.

IR (KBr) cm^{-1} : 3450, 3294, 2941, 1649, 1622, 1599, 1520, 1417, 1319, 1248, 812

30 1H NMR (200MHz, $DMSO-d_6$) δ : 1.40-2.00 (6H, m), 2.35 (3H, s), 2.55-2.67 (2H, m), 2.82-2.95 (5H, m), 3.22-3.35 (4H, m), 4.53 (2H, s), 7.24-7.35 (3H, m), 7.46-7.60 (7H, m), 7.89 (2H, d, $J=8.8Hz$), 10.15 (1H, s).

Working Example 17 (Production of Compound 17)

In DMF (3ml) was dissolved 7-(4-fluorophenyl)-N-[4-(piperidinomethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (500mg), and to the mixture was added methyl

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iodide (212 μ l). The mixture was stirred at room temperature for 18 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 1-[4-[7-(4-fluoro-phenyl)-3,4-dihydro-naphthalene-2-carboxamido]benzyl]-1-methylpiperidinium iodide (Compound 17) (610mg) as colorless crystals.
mp 177-180°C

Elemental Analysis for $C_{30}H_{32}N_2OFI \cdot 0.2H_2O$

Calcd: C, 61.48; H, 5.57; N, 4.78.

10 Found: C, 61.38; H, 5.50; N, 4.81.

IR (KBr) cm^{-1} : 3450, 3310, 2947, 1651, 1597, 1518, 1416, 1319, 1246, 1225, 824

1H NMR (200MHz, DMSO- d_6) δ : 1.40-2.00 (6H, m), 2.55-2.67 (2H, m), 2.85-2.96 (5H, m), 3.20-3.38 (4H, m), 4.53 (2H, s),
15 7.25-7.38 (3H, m), 7.46-7.60 (5H, m), 7.67-7.76 (2H, m), 7.89 (2H, d, $J=8.6Hz$), 10.17 (1H, s).

Working Example 18 (Production of Compound 18)

To a mixture of N-[4-(hydroxymethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (200mg),
20 triethylamine (158 μ l) and THF (10ml) was added methane-sulfonic acid anhydride (118mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was
25 washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in DMF (3ml), and to the mixture was added pyridine (137 μ l). The mixture was stirred at room temperature for 96 hours and concentrated
30 under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)-benzyl]pyridinium chloride (Compound 18) (95mg) as colorless crystals.
mp 162-164°C

35 Elemental Analysis for $C_{29}H_{29}N_2OCl \cdot 1.0H_2O$

Calcd: C, 73.95; H, 5.78; N, 5.95; Cl, 7.53.

Found: C, 74.25; H, 5.94; N, 5.92; Cl, 7.12.

IR (KBr) cm^{-1} : 3450, 3030, 1653, 1595, 1520, 1416, 1323, 1254, 1213, 762

^1H NMR (200MHz, CDCl_3) δ : 2.50-2.75 (4H, m), 5.92 (2H, br s), 7.00 (1H, d, $J=8.0\text{Hz}$), 7.15-7.40 (9H, m), 7.60-7.85 (5H, m), 8.08-8.25 (1H, br), 9.21 (2H, br s), 9.73 (1H, br s).

Working Example 19 (Production of Compound 19)

To a mixture of N-[4-(hydroxymethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (200mg), lithium chloride (95mg), triethylamine (182 μl) and dichloromethane (20ml) was added methanesulfonyl chloride (174 μl), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added dilute hydrochloric acid. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in DMF (3ml), and to the mixture was added 3-picoline (167 μl). The reaction mixture was stirred at room temperature for 17 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3-methyl-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]pyridinium chloride (90mg) as colorless crystals.

mp 136-140°C

Elemental Analysis for $\text{C}_{30}\text{H}_{27}\text{N}_2\text{OCl} \cdot 1.5\text{H}_2\text{O}$

Calcd: C, 72.94; H, 6.12; N, 5.67.

Found: C, 73.19; H, 6.37; N, 5.61.

IR (KBr) cm^{-1} : 3450, 3030, 1653, 1597, 1520, 1416, 1319, 1250, 1213, 764

^1H NMR (200MHz, CDCl_3) δ : 2.48 (3H, s), 2.65-2.90 (4H, m), 6.03 (2H, br s), 7.12-7.20 (1H, m), 7.25-7.55 (9H, m), 7.70-7.82 (4H, m), 7.95-8.07 (1H, m), 9.29 (2H, br s), 9.35-9.50 (1H, br).

Working Example 20 (Production of Compound 20)

To a mixture of N-[4-(hydroxymethyl)phenyl]-7-

phenyl-3,4-dihydronaphthalene-2-carboxamide (200mg), lithium chloride (48mg), triethylamine (158 μ l) and dichloromethane (30ml) was added methanesulfonyl chloride (61 μ l), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added dilute hydrochloric acid. The organic layer was separated, washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in DMF (3ml), and to the mixture was added 3,5-lutidine (193 μ l). The reaction mixture was stirred at room temperature for 65 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3,5-dimethyl-1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 20) (186mg) as colorless crystals.

mp 163-165°C

Elemental Analysis for $C_{21}H_{22}N_2OCl \cdot 1.3H_2O$

Calcd: C, 73.81; H, 6.31; N, 5.55.

Found: C, 73.85; H, 6.29; N, 5.49.

IR (KBr) cm^{-1} : 3450, 3030, 1655, 1597, 1520, 1483, 1416, 1319, 1252, 766

1H NMR (200MHz, $CDCl_3$) δ : 2.44 (6H, s), 2.67-2.92 (4H, m), 5.99 (2H, s), 7.16 (1H, d, $J=7.6Hz$), 7.25-7.55 (9H, m),

7.77-7.90 (4H, m), 9.20 (1H, s), 9.72 (1H, br s).

Working Example 21 (Production of Compound 21)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (140mg), and to the mixture was added 4-cyanopyridine (117mg). The mixture was stirred at 70°C for 24 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 4-cyano-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 21) (141mg) as pale brown crystals.

mp 163-165°C

Elemental Analysis for $C_{30}H_{21}N_3OCl \cdot 0.5H_2O$

Calcd: C, 73.99; H, 5.17; N, 8.63.

Found: C, 73.71; H, 5.29; N, 8.47.

IR (KBr) cm^{-1} : 3430, 3024, 1653, 1597, 1524, 1416, 1319, 1252, 829, 764

1H NMR (200MHz, DMSO- d_6) δ : 2.50-2.65 (2H, m), 2.82-2.93 (2H, m), 5.92 (2H, s), 7.29-7.67 (11H, m), 7.85 (2H, d, $J=8.6Hz$), 8.73 (2H, d, $J=6.8Hz$), 9.54 (2H, d, $J=6.8Hz$), 10.19 (1H, s).

10 Working Example 22 (Production of Compound 22)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added 3-cyanopyridine (133mg). The mixture was stirred at 70°C for 24 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3-cyano-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 22) (58mg) as pale orange crystals.

20 mp 158-161°C

Elemental Analysis for $C_{30}H_{21}N_3OCl \cdot 1.5H_2O$

Calcd: C, 71.35; H, 5.39; N, 8.32.

Found: C, 71.28; H, 5.49; N, 8.40.

IR (KBr) cm^{-1} : 3450, 3028, 1653, 1597, 1520, 1416, 1319, 1252, 766

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1H NMR (200MHz, DMSO- d_6) δ : 2.55-2.68 (2H, m), 2.82-2.95 (2H, m), 5.88 (2H, s), 7.30-7.90 (13H, m), 8.32-8.42 (1H, m), 9.13 (1H, d, $J=8.0Hz$), 9.47 (1H, d, $J=5.8Hz$), 10.05 (1H, s), 10.21 (1H, s).

30 Working Example 23 (Production of Compound 23)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added 3-chloropyridine (122 μ l). The mixture was stirred at 70°C for 24 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3-

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chloro-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 23) (110mg) as pale yellow crystals.
mp 136-139°C

5 Elemental Analysis for $C_{22}H_{19}N_2OCl_2 \cdot 0.5H_2O$

Calcd: C, 70.16; H, 5.08; N, 5.64.

Found: C, 70.13; H, 5.03; N, 5.68.

IR (KBr) cm^{-1} : 3450, 3028, 1653, 1597, 1520, 1483, 1416, 1317, 1252, 1213, 1165, 766, 700

10 1H NMR (200MHz, DMSO- d_6) δ : 2.55-2.68 (2H, m), 2.82-2.95 (2H, m), 5.85 (2H, s), 7.30-7.70 (11H, m), 7.86 (2H, d, $J=8.4Hz$), 8.16-8.26 (1H, m), 8.81 (1H, d, $J=7.6Hz$), 9.24 (1H, d, $J=6.0Hz$), 9.72 (1H, s), 10.21 (1H, s).

Working Example 24 (Production of Compound 24)

15 In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (140mg), and to the mixture was added 1-ethylpiperidine (154 μ l). The mixture was stirred at room temperature for 14 hours and concentrated under reduced pressure. The residue
20 was recrystallized from ethyl acetate-methanol to give 1-ethyl-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]piperidinium chloride (Compound 24) (125mg) as colorless crystals.
mp 153-156°C

25 Elemental Analysis for $C_{31}H_{33}N_2OCl \cdot 1.5H_2O$

Calcd: C, 72.42; H, 7.45; N, 5.45.

Found: C, 72.14; H, 7.41; N, 5.32.

IR (KBr) cm^{-1} : 3450, 2943, 1655, 1595, 1520, 1483, 1416, 1319, 1255, 1217, 766, 700

30 1H NMR (200MHz, $CDCl_3$) δ : 1.30-1.42 (3H, m), 1.60-1.90 (6H, m), 2.68-2.95 (4H, m), 3.27-3.45 (4H, m), 3.55-3.70 (2H, m), 4.75 (2H, s), 7.17 (1H, d, $J=7.8Hz$), 7.25-7.60 (9H, m), 7.90 (1H, s), 8.03 (2H, d, $J=8.6Hz$), 10.00 (1H, s).

Working Example 25 (Production of Compound 25)

35 In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide

(160mg), and to the mixture was added triethylamine (180 μ l). The mixture was stirred at room temperature for 14 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give

- 5 triethyl[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]ammonium chloride (Compound 25) (176mg) as colorless crystals.

mp 205-206°C

Elemental Analysis for $C_{36}H_{33}N_2OCl \cdot 0.2H_2O$

- 10 Calcd: C, 75.28; H, 7.45; N, 5.85.

Found: C, 75.10; H, 7.38; N, 5.91.

IR (KBr) cm^{-1} : 3450, 3007, 1655, 1599, 1519, 1483, 1416, 1319, 1252, 1215, 768, 704

- 1H NMR (200MHz, $CDCl_3$) δ : 1.37 (9H, t, $J=6.9Hz$), 2.72-2.96 (4H, m), 3.22 (6H, q, $J=6.9Hz$), 4.62 (2H, s), 7.15-7.45 (7H, m), 7.50-7.60 (3H, m), 7.99 (1H, s), 8.12 (2H, d, $J=8.6Hz$), 10.19 (1H, s).

Working Example 26 (Production of Compound 26)

- In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added tripropylamine (244 μ l). The mixture was stirred at room temperature for 14 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give [4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)-benzyl]tripropylammonium chloride (Compound 26) (205mg) as colorless crystals.

mp 206-207°C

Elemental Analysis for $C_{33}H_{41}N_2OCl \cdot 0.5H_2O$

- 30 Calcd: C, 75.33; H, 8.05; N, 5.32.

Found: C, 75.59; H, 7.88; N, 5.63.

IR (KBr) cm^{-1} : 3450, 2970, 1649, 1595, 1524, 1481, 1417, 1317, 1252, 1217, 770, 708

- 1H NMR (200MHz, $CDCl_3$) δ : 0.94 (9H, t, $J=7.2Hz$), 1.60-1.90 (6H, m), 2.79-3.10 (10H, m), 4.64 (2H, s), 7.07 (2H, d, $J=8.4Hz$), 7.20 (1H, d, $J=7.8Hz$), 7.31-7.45 (4H, m),

7.54-7.60 (3H, m), 8.10 (1H, s), 8.19 (2H, d, J=8.6Hz), 10.43 (1H, s).

Working Example 27 (Production of Compound 27)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added 3-ethylpyridine (146 μ l). The mixture was stirred at 70°C for 72 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3-ethyl-1-[4-(7-phenyl-3,4-dihydro-naphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 27) (185mg) as colorless crystals.
mp 142-145°C

Elemental Analysis for $C_{31}H_{29}N_2OCl \cdot 0.5H_2O$

Calcd: C, 75.98; H, 6.17; N, 5.72.

Found: C, 75.96; H, 6.13; N, 5.99.

IR (KBr) cm^{-1} : 3381, 1657, 1597, 1520, 1416, 1317, 1252, 762

1H NMR (200MHz, $CDCl_3$) δ : 1.25 (3H, t, J=7.6Hz), 2.64-2.88 (6H, m), 6.09 (2H, s), 7.14 (1H, d, J=7.8Hz), 7.25-7.52 (9H, m), 7.71-7.88 (4H, m), 8.04 (1H, d, J=8.0Hz), 9.37 (1H, d, J=6.0Hz), 9.43 (1H, s), 9.81 (1H, s).

Working Example 28 (Production of Compound 28)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added 2-picoline (126 μ l). The mixture was stirred at 70°C for 63 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 2-methyl-1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 28) (140mg) as pale brown crystals.
mp 152-155°C

Elemental Analysis for $C_{30}H_{27}N_2OCl \cdot 1.0H_2O$

Calcd: C, 74.29; H, 6.03; N, 5.78.

Found: C, 74.56; H, 5.93; N, 5.80.

IR (KBr) cm^{-1} : 3402, 1630, 1597, 1520, 1414, 1319, 1250, 764.

700

¹H NMR (200MHz, CDCl₃) δ: 2.60-2.90 (7H, m), 6.07 (2H, s), 7.04-7.15 (3H, m), 7.25-7.50 (7H, m), 7.65 (1H, d, J=7.8Hz), 7.72-7.92 (4H, m), 8.12-8.22 (1H, m), 9.63 (1H, d, J=6.2Hz), 9.86 (1H, s).

Working Example 29 (Production of Compound 29)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added thiazole (91μl). The mixture was stirred at 100°C for 48 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 3-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]thiazolium chloride (Compound 29) (133mg) as pale brown crystals.

mp 149-152°C

Elemental Analysis for C₂₇H₂₃N₂OSCl · 0.5H₂O

Calcd: C, 69.29; H, 5.17; N, 5.99.

Found: C, 69.43; H, 4.88; N, 6.12.

IR (KBr) cm⁻¹: 3419, 3026, 1649, 1597, 1520, 1414, 1317, 1252, 764, 698

¹H NMR (200MHz, DMSO-d₆) δ: 2.55-2.67 (2H, m), 2.82-2.96 (2H, m), 5.78 (2H, s), 7.29-7.71 (11H, m), 7.84 (2H, d, J=8.2Hz), 8.33-8.40 (1H, m), 8.58-8.66 (1H, m), 10.18 (1H, s), 10.42 (1H, s).

Working Example 30 (Production of Compound 30)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (160mg), and to the mixture was added quinuclidine (285mg). The mixture was stirred at 100°C for 24 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamide)-benzyl]quinuclidium chloride (Compound 30) (62mg) as colorless crystals.

mp 250-252°C

Elemental Analysis for C₃₁H₂₃N₂OC1 · 0.9H₂O

Calcd: C, 74.28; H, 7.00; N, 5.59.

Found: C, 74.48; H, 7.01; N, 5.56.

IR (KBr) cm^{-1} : 3425, 2945, 1655, 1595, 1520, 1416, 1319, 1255, 833, 766, 700

5 ^1H NMR (200MHz, CDCl_3) δ : 1.75-2.15 (7H, m), 2.68-2.90 (4H, m), 3.40-3.70 (6H, m), 4.73 (2H, s), 7.15 (1H, d, $J=7.8\text{Hz}$), 7.25-7.56 (9H, m), 7.88 (1H, s), 7.96 (2H, d, $J=8.0\text{Hz}$), 9.93 (1H, s).

Working Example 31 (Production of Compound 31)

10 In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added ethyl 1-methyl-piperidine-4-carboxylate (206mg). The mixture was stirred at room temperature for 15 hours and concentrated under
15 reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 4-ethoxycarbonyl-1-methyl-1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]piperidinium chloride (Compound 31) (185mg, ratio of isomers=37:63) as colorless crystals.

20 mp 153-156°C

Elemental Analysis for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2\text{Cl} \cdot 0.5\text{H}_2\text{O}$

Calcd: C, 71.53; H, 6.91; N, 5.06.

Found: C, 71.69; H, 6.76; N, 5.11.

IR (KBr) cm^{-1} : 3388, 1726, 1655, 1595, 1520, 1483, 1416, 1319,
25 1254, 1214, 766, 700

^1H NMR (200MHz, CDCl_3) δ : 1.15-1.30 (3H, m), 2.05-2.22 (3H, m), 2.65-2.92 (6H, m), 3.02 (1.11H, s), 3.13 (1.89H, s), 3.38-3.75 (3.26H, m), 3.88-4.22 (2.74H, m), 4.76 (1.26H, s), 5.09 (0.74H, s), 7.15 (1H, dd, $J=4.4, 7.6\text{Hz}$), 7.25-
30 7.55 (9H, m), 7.83 (1H, s), 7.94 (1H, d, $J=8.4\text{Hz}$), 8.00 (1H, d, $J=8.4\text{Hz}$), 9.74 (0.63H, s), 9.84 (0.37H, s).

Working Example 32 (Production of Compound 32)

In THF (10ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide
35 (300mg), and to the mixture was added hexamethyleneimine (270 μl). The mixture was refluxed for 3.5 hours. The

reaction mixture was cooled to room temperature, and to the mixture was added water (30ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/triethylamine=20/1) and recrystallized from ethyl acetate-hexane to give N-[4-(1-perhydroazepinylmethyl)-phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (Compound 32) (257mg) as colorless crystals.

mp 168-170°C

Elemental Analysis for $C_{30}H_{32}N_2O$

Calcd: C, 82.53; H, 7.39; N, 6.42.

Found: C, 82.28; H, 7.26; N, 6.37.

IR (KBr) cm^{-1} : 3304, 2924, 1645, 1601, 1520, 1410, 1317, 1254, 831, 762, 698

1H NMR (200MHz, $CDCl_3$) δ : 1.61 (8H, s), 2.56-2.76 (6H, m), 2.92-3.03 (2H, m), 3.61 (2H, s), 7.23-7.61 (14H, m).

Working Example 33 (Production of Compound 33)

In DMF (3ml) was dissolved N-[4-(1-perhydroazepinylmethyl)phenyl]-7-phenyl-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added methyl iodide (64 μ l). The mixture was stirred at room temperature for 12 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give 1-methyl-1-[4-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]perhydro-azepinium iodide (180mg) as colorless crystals.

mp 197-199°C

Elemental Analysis for $C_{31}H_{33}N_2OI \cdot 0.5H_2O$

Calcd: C, 63.37; H, 6.18; N, 4.77.

Found: C, 63.39; H, 6.31; N, 4.71.

IR (KBr) cm^{-1} : 3427, 3267, 2937, 1660, 1593, 1520, 1481, 1417, 1313, 1250, 694

1H NMR (200MHz, DMSO- d_6) δ : 1.50-1.70 (4H, m), 1.80-1.96 (4H,

m), 2.55-2.68 (2H, m), 2.83-2.97 (5H, m), 3.22-3.36 (2H, m), 3.40-3.60 (2H, m), 4.50 (2H, s), 7.30-7.70 (11H, m), 7.89 (2H, d, J=8.4Hz), 10.19 (1H, s).

Working Example 34 (Production of Compound 34)

- 5 In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 1-ethylpiperidine (159 μ l). The mixture was stirred at room temperature for 20 hours. To the reaction mixture was added
10 ethyl acetate (100ml), and the resulting precipitate was filtered to give 1-ethyl-1-[4-[7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]piperidinium chloride (Compound 34) (156mg) as colorless crystals.
mp 207-209°C

- 15 Elemental Analysis for $C_{22}H_{21}N_2OCl$

Calcd: C, 76.70; H, 7.44; N, 5.59.

Found: C, 76.33; H, 7.22; N, 5.67.

IR (KBr) cm^{-1} : 3440, 2945, 1651, 1595, 1520, 1416, 1321, 1248, 808

- 20 1H NMR (200MHz, $CDCl_3$) δ : 1.36 (3H, t, J=6.0Hz), 1.60-1.90 (6H, m), 2.37 (3H, s), 2.68-2.92 (4H, m), 3.26-3.42 (4H, m), 3.52-3.70 (2H, m), 4.76 (2H, s), 7.11-7.23 (3H, m), 7.31-7.52 (6H, m), 7.90 (1H, s), 8.04 (2H, d, J=8.4Hz), 10.07 (1H, s).

- 25 Working Example 35 (Production of Compound 35)

- In THF (15ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (300mg), and to the mixture was added 4-benzylpiperidine (408 μ l). The mixture was refluxed for 19
30 hours. The reaction mixture was cooled to room temperature, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced
35 pressure. The residue was separated and purified with column chromatography (ethyl acetate) and recrystallized

from ethyl acetate-hexane to give N-[4-(4-benzyl-piperidinomethyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 35) (259mg) as colorless crystals.

5 mp 199-201°C

Elemental Analysis for $C_{27}H_{30}N_2O$

Calcd: C, 84.37; H, 7.27; N, 5.32.

Found: C, 84.34; H, 7.18; N, 5.39.

IR (KBr) cm^{-1} : 3439, 2920, 1647, 1520, 1412, 1315, 808, 700

10 1H NMR (200MHz, $CDCl_3$) δ : 1.20-1.70 (5H, m), 1.80-1.97 (2H, m), 2.40 (3H, s), 2.53 (2H, d, $J=6.2Hz$), 2.65-2.78 (2H, m), 2.80-3.02 (4H, m), 3.45 (2H, s), 7.09-7.36 (11H, m), 7.40-7.63 (7H, m).

Working Example 36 (Production of Compound 36)

15 In DMF (3ml) was dissolved N-[4-(4-benzyl-piperidino-methyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added methyl iodide (53 μ l). The mixture was stirred at room temperature for 23 hours. To the reaction mixture was added
20 ethyl acetate(100ml), and the resulting precipitate was filtered to give 4-benzyl-1-methyl-1-[4-[7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]-piperidinium iodide (Compound 36) (141mg, ratio of isomers=19:81) as colorless crystals.

25 mp 209-212°C

Elemental Analysis for $C_{30}H_{34}N_2OI \cdot 0.5H_2O$

Calcd: C, 67.35; H, 6.25; N, 4.13.

Found: C, 67.28; H, 6.33; N, 4.08.

IR (KBr) cm^{-1} : 3439, 1659, 1593, 1520, 1416, 1317, 1250, 812

30 1H NMR (200MHz, $DMSO-d_6$) δ : 1.55-2.00 (5H, m), 2.35 (3H, s), 2.52-2.75 (4H, m), 2.80-3.00 (5H, m), 3.20-3.40 (4H, m), 4.49 (1.62H, s), 4.60 (0.38H, s), 7.13-7.60 (15H, m), 7.80-7.90 (2H, m), 10.15 (1H, s).

Working Example 37 (Production of Compound 37)

35 In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-

carboxamide (150mg), and to the mixture was added 1-ethylperhydroazepine (98mg). The mixture was stirred at room temperature for 15 hours. To the reaction mixture was added ethyl acetate (100ml), and the resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give 1-ethyl-1-[4-[7-(4-methyl-phenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]perhydroazepinium chloride (Compound 37) (137mg) as colorless crystals.

mp 207-210°C

Elemental Analysis for $C_{23}H_{29}N_2OCl \cdot 0.5H_2O$

Calcd: C, 75.62; H, 7.69; N, 5.34.

Found: C, 75.82; H, 7.69; N, 5.42.

IR (KBr) cm^{-1} : 3431, 2931, 1653, 1597, 1520, 1325, 1255, 808

1H NMR (200MHz, DMSO- d_6) δ : 1.40 (3H, t, $J=7.1Hz$), 1.50-1.65 (4H, m), 1.70-1.90 (4H, m), 2.35 (3H, s), 2.55-2.67 (2H, m), 2.80-2.93 (2H, m), 3.12-3.35 (4H, m), 3.40-3.57 (2H, m), 4.47 (2H, s), 7.23-7.35 (3H, m), 7.50-7.60 (7H, m), 7.91 (2H, d, $J=8.4Hz$), 10.26 (1H, s).

Working Example 38 (Production of Compound 38)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 1-propylperhydroazepine (109mg). The mixture was stirred at room temperature for 15 hours. To the reaction mixture was added ethyl acetate (100ml), and the resulting precipitate was filtered to give 1-[4-[7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]-1-propylperhydroazepinium chloride (Compound 38) (163mg) as colorless crystals.

mp 195-199°C

Elemental Analysis for $C_{24}H_{31}N_2OCl \cdot 0.5H_2O$

Calcd: C, 75.88; H, 7.87; N, 5.21.

Found: C, 76.07; H, 7.83; N, 5.21.

IR (KBr) cm^{-1} : 3423, 2937, 1651, 1595, 1520, 1317, 1250, 814

1H NMR (200MHz, DMSO- d_6) δ : 0.93 (3H, t, $J=7.2Hz$), 1.52-

1.65 (4H, m), 1.75-1.93 (6H, m), 2.35 (3H, s), 2.55-2.68 (2H, m), 2.80-2.95 (2H, m), 3.00-3.13 (2H, m), 3.22-3.40 (2H, m), 3.40-3.58 (2H, m), 4.49 (2H, s), 7.23-7.35 (3H, m), 7.46-7.60 (7H, m), 7.90 (2H, d, J=8.0Hz), 10.22 (1H, s).

Working Example 39 (Production of Compound 39)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 1-ethylperhydroazocine (109mg). The mixture was stirred at room temperature for 14 hours. To the reaction mixture was added ethyl acetate (100ml), and the resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give 1-ethyl-1-[4-[7-(4-methyl-phenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]perhydro-

azocinium chloride (Compound 39) (142mg) as colorless crystals.

mp 197-199°C

Elemental Analysis for $C_{21}H_{21}N_2OCl \cdot 0.5H_2O$

Calcd: C, 75.88; H, 7.87; N, 5.21.

Found: C, 75.67; H, 7.88; N, 5.30.

IR (KBr) cm^{-1} : 3437, 2926, 1655, 1595, 1520, 1489, 1416, 1321, 1252, 812

1H NMR (200MHz, DMSO- d_6) δ : 1.30-2.00 (13H, m), 2.35 (3H, s), 2.55-2.70 (2H, m), 2.85-3.00 (2H, m), 3.05-3.50 (6H, m), 4.44 (2H, s), 7.20-7.37 (3H, m), 7.40-7.60 (7H, m), 7.92 (2H, d, J=8.6Hz), 10.28 (1H, s).

Working Example 40 (Production of Compound 40)

In THF (7ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydro-naphthalene-2-carboxamide (150mg), and to the mixture was added 1-methylpiperazine (129 μ l). The mixture was refluxed for 24 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium

(100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give N-[4-(piperidinomethyl)phenyl]-7-phenylnaphthalene-2-carboxamide (Compound 58) (491mg) as pale yellow crystals. mp 177-178°C

Elemental Analysis for $C_{29}H_{28}N_2O \cdot 0.2H_2O$

Calcd: C, 82.12; H, 6.75; N, 6.60.

Found: C, 82.26; H, 6.80; N, 6.62.

IR (KBr) cm^{-1} : 3313, 2933, 1649, 1527, 1317, 849, 754, 692

1H NMR (200MHz, $CDCl_3$) δ : 1.37-1.65 (6H, m), 2.35-2.45 (4H, m), 3.48 (2H, s), 7.33-7.57 (5H, m), 7.62-7.77 (4H, m),

7.83-8.01 (5H, m), 8.15 (1H, s), 8.44 (1H, s).

Working Example 59 (Production of Compound 59)

In DMF (3ml) was dissolved N-[4-(piperidinomethyl)phenyl]-7-phenylnaphthalene-2-carboxamide (300mg), and to the mixture was added methyl iodide (133 μ l). The mixture was stirred at room temperature for 16 hours and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 1-[4-(7-phenylnaphthalene-2-carboxamido)benzyl]-1-methylpiperidinium iodide (Compound 59) (374mg) as pale yellow crystals.

mp 203-207°C

Elemental Analysis for $C_{30}H_{31}N_2OI \cdot 1.0H_2O$

Calcd: C, 62.07; H, 5.73; N, 4.83.

Found: C, 61.82; H, 5.43; N, 4.87.

IR (KBr) cm^{-1} : 3450, 1655, 1597, 1520, 1417, 1317, 1250, 700

1H NMR (200MHz, $DMSO-d_6$) δ : 1.40-2.00 (6H, m), 2.94 (3H, s), 3.25-3.40 (4H, m), 4.56 (2H, s), 7.40-7.60 (5H, m), 7.84-7.89 (2H, m), 7.95-8.17 (6H, m), 8.40 (1H, s), 8.66 (1H, s), 10.68 (1H, s).

Working Example 60 (Production of Compound 60)

In THF (15ml) was dissolved 5-(4-methylphenyl)-indene-2-carboxylic acid (500mg), and to the solution were

added oxalyl chloride (262 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (15ml), and to the solution were added
5 1-(4-aminobenzyl)piperidine (419mg) and triethylamine (336 μ l) at room temperature. The reaction mixture was stirred at room temperature for 16 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium
10 chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give N-[4-(piperidinomethyl)phenyl]-5-(4-methylphenyl)-indene-2-carboxamide (Compound 60) (549mg) as colorless crystals.
15 mp 219-220°C

Elemental Analysis for $C_{27}H_{30}N_2O$

Calcd: C, 82.43; H, 7.16; N, 6.63.

Found: C, 82.17; H, 7.13; N, 6.56.

IR (KBr) cm^{-1} : 3346, 2935, 1645, 1597, 1516, 1408, 1315, 1250,
20 808

1H NMR (200MHz, DMSO- d_6) δ : 1.34-1.57 (6H, m), 2.25-2.40 (7H, m), 3.30-3.43 (2H, m), 3.80-3.90 (2H, m), 7.20-7.32 (4H, m), 7.56-7.68 (4H, m), 7.72 (2H, d, $J=8.4Hz$), 7.83 (2H, s), 9.96 (1H, s).

25 Working Example 61 (Production of Compound 61)

In DMF (10ml) was dissolved N-[4-(piperidinomethyl)-phenyl]-5-(4-methylphenyl)indene-2-carboxamide (400mg), and to the mixture was added methyl iodide (177 μ l). The mixture was stirred at room temperature for 86 hours and
30 concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 1-[4-[5-(4-methylphenyl)indene-2-carboxamido]-benzyl]-1-methyl-piperidinium iodide (Compound 61) (516mg) as pale yellow crystals.

35 mp 199-201°C

Elemental Analysis for $C_{30}H_{33}N_2OI \cdot 0.5H_2O$

Calcd: C, 62.83; H, 5.98; N, 4.88.

Found: C, 62.56; H, 5.87; N, 4.97.

IR (KBr) cm^{-1} : 3450, 2947, 1651, 1595, 1520, 1416, 1322, 1246, 808

5 ^1H NMR (200MHz, DMSO-d_6) δ : 1.40-2.00 (6H, m), 2.36 (3H, s), 2.92 (3H, s), 3.20-3.40 (4H, m), 3.80-3.90 (2H, m), 4.54 (2H, s), 7.30 (2H, d, $J=8.0\text{Hz}$), 7.52 (2H, d, $J=8.0\text{Hz}$), 7.55-7.70 (4H, m), 7.85-7.97 (4H, m), 10.20-10.25 (1H, m).

Working Example 62 (Production of Compound 62)

10 In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the solution were added 1-(4-methoxyphenyl)piperazine dihydrochloride (190mg) and potassium carbonate (382mg). The mixture was stirred at room temperature for 14 hours, 15 and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl 20 acetate-diisopropylether to give (E)-N-[4-[1-(4-methoxyphenyl)-4-piperazinylmethyl]phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 62) (224mg) as colorless crystals. mp 207-208°C

Elemental Analysis for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_2$

25 Calcd: C, 78.89; H, 6.81; N, 8.12.

Found: C, 78.59; H, 6.65; N, 8.13.

IR (KBr) cm^{-1} : 2937, 2812, 1662, 1626, 1512, 1248, 820, 795

^1H NMR (200MHz, CDCl_3) δ : 2.41 (3H, s), 2.56-2.65 (4H, m), 3.04-3.13 (4H, m), 3.54 (2H, s), 3.76 (3H, s), 6.61 (1H, 30 d, $J=15.6\text{Hz}$), 6.78-6.94 (4H, m), 7.23-7.63 (12H, m), 7.73 (1H, s), 7.82 (1H, d, $J=15.6\text{Hz}$).

Working Example 63 (Production of Compound 63)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the 35 solution were added 2-(3,4-dimethoxyphenyl)ethylmethylamine (132 μl) and potassium carbonate (382mg). The mixture

was stirred at room temperature for 12 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate) to give colorless amorphous, which was dissolved in ethyl acetate (50ml), and to the mixture was added 4N hydrochloric acid ethyl acetate solution (0.5ml). The resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give (E)-N-[4-[N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylaminomethyl]phenyl]-3-(4-methylphenyl)cinnamamide hydrochloride (Compound 63) (245mg) as colorless crystals. mp 214-217°C

Elemental Analysis for $C_{24}H_{28}N_2O_3 \cdot 1.0HCl$

Calcd: C, 73.30; H, 6.69; N, 5.03; Cl, 6.36.

Found: C, 73.00; H, 6.66; N, 4.99; Cl, 6.20.

IR (KBr) cm^{-1} : 3427, 2941, 1682, 1601, 1518, 1417, 1344, 1259, 1174, 1026, 793

1H NMR (200MHz, DMSO- d_6) δ : 2.37 (3H, s), 2.66-2.75 (3H, m), 2.95-3.40 (4H, m), 3.73 (3H, s), 3.75 (3H, s), 4.15-4.28 (1H, m), 4.32-4.46 (1H, m), 6.77 (1H, dd, $J=1.8, 8.2Hz$), 6.84-6.94 (2H, m), 7.02 (1H, d, $J=16.0Hz$), 7.31 (2H, d, $J=7.8Hz$), 7.48-7.75 (8H, m), 7.79-7.93 (3H, m), 10.56 (2H, s).

Working Example 64 (Production of Compound 64)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the solution were added methylaminoacetonitrile hydrochloride (77mg) and potassium carbonate (382mg). The mixture was stirred at room temperature for 14 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The

residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-[N-(cyanomethyl)-N-methylaminomethyl]phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 64) (129mg) as colorless crystals.

5 mp 163-165°C

Elemental Analysis for $C_{26}H_{23}N_3O \cdot 0.1H_2O$

Calcd: C, 78.60; H, 6.39; N, 10.58.

Found: C, 78.44; H, 6.32; N, 10.35.

10 IR (KBr) cm^{-1} : 3250, 3055, 1662, 1626, 1599, 1535, 1516, 1412, 1344, 1184, 982, 822, 791

1H NMR (200MHz, $CDCl_3$) δ : 2.42 (3H, s), 2.44 (3H, s), 3.46 (2H, s), 3.59 (2H, s), 6.61 (1H, d, $J=15.4Hz$), 7.23-7.65 (12H, m), 7.74 (1H, s), 7.83 (1H, d, $J=15.4Hz$).

Working Example 65 (Production of Compound 65)

15 In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the solution were added imidazole (49mg) and potassium carbonate (382mg). The mixture was stirred at room temperature for 18 hours, and to the mixture was added water. The mixture
20 was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-[(imidazol-1-yl)methyl]phenyl]-3-(4-methylphenyl)-cinnamamide
25 (Compound 65) (90mg) as colorless crystals.
mp 198-200°C

Elemental Analysis for $C_{26}H_{23}N_3O \cdot 0.3H_2O$

Calcd: C, 78.29; H, 5.96; N, 10.53.

30 Found: C, 78.26; H, 5.92; N, 10.17.

IR (KBr) cm^{-1} : 3026, 1674, 1628, 1601, 1539, 1518, 1416, 1342, 1182, 1080, 787

1H NMR (200MHz, $CDCl_3$) δ : 2.41 (3H, s), 5.08 (2H, s), 6.67 (1H, d, $J=15.4Hz$), 6.91 (1H, s), 7.09-7.16 (3H, m), 7.23-7.30

35 (2H, m), 7.35-7.66 (8H, m), 7.72 (1H, s), 7.82 (1H, d, $J=15.4Hz$), 8.00 (1H, br s).

Working Example 66 (Production of Compound 66)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the solution were added 3-(hydroxymethyl)piperidine (191mg).
5 The mixture was stirred at room temperature for 72 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced
10 pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-[3-(hydroxymethyl)piperidinomethyl]phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 66) (160mg) as colorless crystals. mp 153-154°C

15 Elemental Analysis for $C_{22}H_{22}N_2O_2 \cdot 0.1H_2O$

Calcd: C, 78.74; H, 7.34; N, 6.33.

Found: C, 78.51; H, 7.32; N, 6.25.

IR (KBr) cm^{-1} : 3290, 2924, 1664, 1626, 1603, 1543, 1514, 1412, 1346, 1186, 789

20 1H NMR (200MHz, $CDCl_3$) δ : 1.50-1.90 (3H, m), 2.05-2.35 (4H, m), 2.41 (3H, s), 2.50-2.63 (1H, m), 2.70-2.80 (1H, m), 3.46 (2H, s), 3.50-3.71 (2H, m), 6.65 (1H, d, $J=15.6Hz$), 7.23-7.31 (4H, m), 7.36-7.61 (7H, m), 7.70-7.87 (3H, m).

Working Example 67 (Production of Compound 67)

25 In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the mixture was added 3-hydroxypiperidine (168mg). The mixture was stirred at room temperature for 13 hours, and to the mixture was added water (50ml). The mixture was extracted
30 with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-(3-hydroxypiperidino-
35 methyl)phenyl]-3-(4-methylphenyl)cinnamamide (Compound 67) (174mg) as colorless crystals.

mp 132-134°C

Elemental Analysis for $C_{28}H_{30}N_2O_2$

Calcd: C, 78.84; H, 7.09; N, 6.57.

Found: C, 78.58; H, 7.08; N, 6.54.

5 IR (KBr) cm^{-1} : 3427, 2937, 1660, 1628, 1601, 1539, 1412, 1344, 1184, 791

1H NMR (200MHz, DMSO- d_6) δ : 1.28-1.90 (6H, m), 2.36 (3H, s), 2.59-2.68 (1H, m), 2.72-2.85 (1H, m), 3.33 (2H, s), 4.56 (1H, d, $J=4.8Hz$), 6.93 (1H, d, $J=15.8Hz$), 7.20-7.35 (4H, m), 7.46-7.71 (8H, m), 7.89 (1H, s), 10.19 (1H, s).

10 Working Example 68 (Production of Compound 68)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the mixture was added 2-piperidinemethanol (191mg). The mixture was stirred at room temperature for 13 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-[2-(hydroxymethyl)piperidinomethyl]phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 68) (120mg) as colorless crystals. mp 137-139°C

25 Elemental Analysis for $C_{29}H_{32}N_2O_2$

Calcd: C, 79.06; H, 7.32; N, 6.36.

Found: C, 78.73; H, 7.38; N, 6.37.

IR (KBr) cm^{-1} : 3325, 2922, 1664, 1630, 1601, 1531, 1412, 1338, 1174, 974, 793

30 1H NMR (200MHz, $CDCl_3$) δ : 1.30-1.80 (6H, m), 2.10-2.25 (1H, m), 2.40-2.57 (1H, m), 2.41 (3H, s), 2.82-2.93 (1H, m), 3.33 (1H, d, $J=13.5Hz$), 3.53 (1H, dd, $J=4.0, 10.8Hz$), 3.88 (1H, dd, $J=4.0, 10.8Hz$), 4.04 (1H, d, $J=13.5Hz$), 6.61 (1H, d, $J=15.4Hz$), 7.23-7.33 (4H, m), 7.37-7.62 (8H, m), 7.74 (1H, s), 7.82 (1H, d, $J=15.4Hz$).

35 Working Example 69 (Production of Compound 69)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the mixture was added 2-(2-hydroxyethyl)piperidine (214mg). The mixture was stirred at room temperature for 18 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-[2-(2-hydroxyethyl)piperidinomethyl]phenyl]-3-(4-methylphenyl)cinnamamide (Compound 69) (202mg) as colorless crystals.

mp 142-143°C

15 Elemental Analysis for $C_{20}H_{24}N_2O_2$

Calcd: C, 79.26; H, 7.54; N, 6.16.

Found: C, 79.00; H, 7.27; N, 6.19.

IR (KBr) cm^{-1} : 3300, 2935, 1666, 1628, 1603, 1541, 1516, 1412, 1344, 1182, 789

20 ^1H NMR (200MHz, CDCl_3) δ : 1.30-2.13 (8H, m), 2.20-2.35 (1H, m), 2.41 (3H, s), 2.73-2.87 (1H, m), 2.92-3.07 (1H, m), 3.48 (1H, d, $J=13.0\text{Hz}$), 3.70-3.83 (1H, m), 3.90-4.02 (1H, m), 4.14 (1H, d, $J=13.0\text{Hz}$), 6.65 (1H, d, $J=15.4\text{Hz}$), 7.23-7.33 (4H, m), 7.38-7.64 (7H, m), 7.72-7.87 (3H, m).

25 Working Example 70 (Production of Compound 70)

In THF (10ml) was dissolved 3-(4-methylphenyl)-cinnamic acid (0.48g), and to the solution were added oxalyl chloride (0.35ml) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (20ml), and to the solution were added 1-(4-aminobenzyl)piperidine (0.38g) and triethylamine (0.34ml) at room temperature. The reaction mixture was stirred at room temperature for 2 hours, and to the mixture was added water (150ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried

with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give (E)-N-[4-(piperidinomethyl)-phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 70) (0.60g) as pale yellow crystals. mp 154-156°C

Elemental Analysis for $C_{28}H_{30}N_2O \cdot 0.4H_2O$

Calcd: C, 80.50; H, 7.43; N, 6.71.

Found: C, 80.60; H, 7.28; N, 6.52.

¹H NMR (200MHz, CDCl₃) δ : 1.44 (2H, m), 1.58 (4H, m), 2.39 (4H, m), 2.41 (3H, s), 3.47 (2H, s), 6.61 (1H, d, J=15.6Hz), 7.25-7.60 (12H, m), 7.73 (1H, s), 7.82 (1H, d, J=15.6Hz). Working Example 71 (Production of Compound 71)

In THF (10ml) was dissolved 3-(2-methylphenyl)-cinnamic acid (0.48g), and to the solution were added oxalyl chloride (0.35ml) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (20ml), and to the solution were added 1-(4-aminobenzyl)piperidine (0.38g) and triethylamine (0.34ml) at room temperature.

The reaction mixture was stirred at room temperature for 2 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was washed with ethyl acetate-diisopropylether to give (E)-N-[4-(piperidinomethyl)phenyl]-3-(2-methyl-phenyl)-cinnamamide (Compound 71) (0.75g) as pale yellow amorphous.

Elemental Analysis for $C_{28}H_{30}N_2O \cdot 0.5H_2O$

Calcd: C, 80.16; H, 7.45; N, 6.68.

Found: C, 80.15; H, 7.38; N, 6.64.

¹H NMR (200MHz, CDCl₃) δ : 1.45 (2H, m), 1.58 (4H, m), 2.27 (3H, s), 2.39 (2H, m), 3.47 (2H, s), 6.58 (1H, d, J=15.4Hz), 7.24-7.35 (7H, m), 7.39-7.58 (6H, m), 7.80 (1H, d, J=15.6Hz). Working Example 72 (Production of Compound 72)

In DMF (4ml) was dissolved (E)-N-[4-(piperidino-methyl)phenyl]-3-(4-methylphenyl)cinnamamide (0.41g), and to the mixture was added methyl iodide (0.43g). The mixture was stirred at room temperature for 20 hours and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to give (E)-1-methyl-1-[4-(3-(4-methylphenyl)cinnamamido)benzyl]-piperidinium iodide (Compound 72) (0.51g) as pale yellow crystals.
mp 176-178°C

10 Elemental Analysis for $C_{29}H_{33}N_2OI \cdot 1.5H_2O$

Calcd: C, 60.10; H, 6.26; N, 4.83.

Found: C, 60.19; H, 6.25; N, 4.95.

1H NMR (200MHz, DMSO- d_6) δ : 1.62 (2H, m), 1.88 (4H, m), 2.37 (3H, s), 2.93 (3H, s), 3.36 (4H, m), 4.55 (2H, s), 6.97 (1H, d, J=15.8Hz), 7.31 (2H, d, J=7.6Hz), 7.50-7.90 (11H, m), 10.44 (1H, s).

Working Example 73 (Production of Compound 73)

In DMF (6ml) was dissolved (E)-N-[4-(piperidino-methyl)phenyl]-3-(2-methylphenyl)cinnamamide (0.62g), and to the mixture was added methyl iodide (0.64g). The mixture was stirred at room temperature for 20 hours and concentrated under reduced pressure. The residue was solidified with ethyl acetate to give (E)-1-methyl-1-[4-(3-(2-methylphenyl)cinnamamido)benzyl]-piperidinium iodide (Compound 73) (0.79g) as pale yellow amorphous.

25 Elemental Analysis for $C_{28}H_{31}N_2OI \cdot 1.5H_2O$

Calcd: C, 60.10; H, 6.26; N, 4.83.

Found: C, 60.00; H, 6.11; N, 5.00.

1H NMR (200MHz, DMSO- d_6) δ : 1.62 (2H, m), 1.88 (4H, m), 2.27 (3H, s), 2.93 (3H, s), 3.32 (4H, m), 4.56 (2H, s), 6.94 (1H, d, J=15.6Hz), 7.27-7.73 (11H, m), 7.84 (2H, d, J=8.4Hz), 10.40 (1H, s).

Working Example 74 (Production of Compound 74)

In THF (10ml) was dissolved 3-(2,5-dimethylphenyl)-cinnamic acid (0.50g), and to the solution were added oxalyl chloride (0.35ml) and a drop of DMF. The mixture was stirred

- at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (20ml), and to the solution were added 1-(4-aminobenzyl)piperidine (0.38g) and triethylamine (0.34ml) at room temperature.
- 5 The reaction mixture was stirred at room temperature for 2 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under
- 10 reduced pressure. The residue was washed with ethyl acetate-diisopropylether to give (E)-N-[4-(piperidino-methyl)phenyl]-3-(2,5-dimethylphenyl)cinnamamide (Compound 74) (0.75g) as pale yellow amorphous.
- Elemental Analysis for $C_{22}H_{22}N_2O \cdot 0.5H_2O$
- 15 Calcd: C, 80.33; H, 7.67; N, 6.46.
Found: C, 80.25; H, 7.34; N, 6.68.
- 1H NMR (200MHz, $CDCl_3$) δ : 1.44 (2H, m), 1.61 (4H, m), 2.22 (3H, s), 2.36 (3H, s), 2.47 (4H, m), 3.55 (2H, s), 6.61 (1H, d, $J=15.4Hz$), 7.05-7.20 (3H, m), 7.28-7.60 (8H, m), 7.71
- 20 (1H, s), 7.79 (1H, d, $J=15.4Hz$).
- Working Example 75 (Production of Compound 75)
- In THF (10ml) was dissolved 3-(3-nitrophenyl)cinnamic acid (0.54g), and to the solution were added oxalyl chloride (0.35ml) and a drop of DMF. The mixture was stirred at room
- 25 temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (20ml), and to the solution were added 1-(4-aminobenzyl)piperidine (0.38g) and triethylamine (0.34ml) at room temperature. The reaction mixture was stirred at room temperature for
- 30 2 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from
- 35 ethyl acetate to give (E)-N-[4-(piperidinomethyl)-phenyl]-3-(3-nitrophenyl)cinnamamide (Compound 75)

(0.65g) as pale yellow crystals.

mp 178-179°C

Elemental Analysis for $C_{27}H_{27}N_2O_3 \cdot 0.5H_2O$

Calcd: C, 71.98; H, 6.26; N, 9.33.

5 Found: C, 71.69; H, 6.38; N, 9.44.

1H NMR (200MHz, DMSO- d_6) δ : 1.51 (6H, m), 2.33 (4H, m), 3.39 (2H, s), 6.96 (1H, d, $J=15.8Hz$), 7.24 (2H, d, $J=8.0Hz$), 7.59-7.83 (7H, m), 8.02 (1H, s), 8.18-8.30 (2H, m), 8.52 (1H, s), 10.18 (1H, s).

10 Working Example 76 (Production of Compound 76)

In DMF (6ml) was dissolved (E)-N-[4-(piperidino-methyl)phenyl]-3-(2,5-dimethylphenyl)cinnamamide (0.60g), and to the mixture was added methyl iodide (0.60g). The mixture was stirred at room temperature for 20 hours and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to give (E)-1-methyl-1-[4-(3-(2,5-dimethylphenyl)cinnamamido)benzyl]-piperidinium iodide (Compound 76) (0.66g) as pale yellow crystals.

20 mp 145-147°C

Elemental Analysis for $C_{30}H_{33}N_2OI \cdot 1.5H_2O$

Calcd: C, 60.71; H, 6.45; N, 4.72.

Found: C, 61.06; H, 6.10; N, 4.74.

1H NMR (200MHz, DMSO- d_6) δ : 1.62 (2H, m), 1.88 (4H, m), 2.22 (3H, s), 2.33 (3H, s), 2.93 (3H, s), 3.33 (4H, m), 4.55 (2H, s), 6.92 (1H, d, $J=15.8Hz$), 7.07 (1H, s), 7.15 (2H, ABq, $J=7.6Hz$), 7.37 (1H, d, $J=7.4Hz$), 7.48-7.60 (5H, m), 7.67 (1H, d, $J=15.6Hz$), 7.84 (2H, d, $J=8.4Hz$), 10.39 (1H, s).

Working Example 77 (Production of Compound 77)

30 In DMF (6ml) was dissolved (E)-N-[4-(piperidino-methyl)phenyl]-3-(3-nitrophenyl)cinnamamide (0.59g), and to the mixture was added methyl iodide (0.57g). The mixture was stirred at room temperature for 20 hours and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to give (E)-1-methyl-1-[4-(3-(3-nitro-phenyl)cinnamamido)benzyl]-piperidinium iodide (Compound

77) (0.75g) as pale yellow crystals.

mp 188-190°C

Elemental Analysis for $C_{26}H_{30}N_3O_3I \cdot 1.5H_2O$

Calcd: C, 55.09; H, 5.45; N, 6.88.

5 Found: C, 54.91; H, 5.40; N, 7.23.

1H NMR (200MHz, DMSO- d_6) δ : 1.65 (2H, m), 1.90 (4H, m), 2.94 (3H, s), 3.35 (4H, m), 4.56 (2H, s), 6.99 (1H, d, $J=15.8Hz$), 7.49-7.88 (9H, m), 8.04 (1H, s), 8.18-8.29 (2H, m), 8.53 (1H, s), 10.45 (1H, s).

10 Working Example 78 (Production of Compound 78)

In toluene(10ml) was dissolved (E)-N-[4-(chloromethyl)phenyl]-3-(4-methylphenyl)cinnamamide (300mg), and to the mixture was added tributylphosphine (248 μ l). The mixture was stirred at 80°C for 3 days and cooled to room temperature. The resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give (E)-tributyl[4-[3-(4-methylphenyl)cinnamamido]benzyl]-phosphonium chloride (Compound 78) (389mg) as colorless crystals.

20 mp 216-217°C

Elemental Analysis for $C_{26}H_{30}NOClP$

Calcd: C, 74.51; H, 8.40; N, 2.48.

Found: C, 74.40; H, 8.33; N, 2.63.

IR (KBr) cm^{-1} : 3429, 2966, 1674, 1630, 1601, 1537, 1516, 1344,

25 1180, 789

1H NMR (200MHz, DMSO- d_6) δ : 0.85-1.00 (9H, m), 1.30-1.60 (12H, m), 2.05-2.25 (6H, m), 2.37 (3H, s), 3.79 (2H, d, $J=15.2Hz$), 7.05 (1H, d, $J=15.8Hz$), 7.25-7.35 (4H, m), 7.48-7.90 (9H, m), 10.61 (1H, s).

30 Working Example 79 (Production of Compound 79)

In THF (10ml) was dissolved (E)-3-(4-methylphenyl)-cinnamic acid (400mg), and to the solution were added oxalyl chloride (220 μ l) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the mixture was dropwise added a solution of (4-aminophenyl)

(2-pyridyl)methanol (370mg) and triethylamine (471 μ l) in THF (15ml) at 0°C. The reaction mixture was stirred at room temperature for 20 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give (E)-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-3-(4-methylphenyl)cinnamamide (Compound 79) (517mg) as colorless crystals.

mp 162-165°C

Elemental Analysis for $C_{22}H_{24}N_2O_2 \cdot 0.1H_2O$

Calcd: C, 79.63; H, 5.78; N, 6.63.

Found: C, 79.53; H, 5.73; N, 6.58.

IR (KBr) cm^{-1} : 3257, 1659, 1626, 1597, 1531, 1410, 1342, 1250, 1182, 787, 758

1H NMR (200MHz, $CDCl_3$) δ : 2.41 (3H, s), 5.27-5.36 (1H, m), 5.70-5.77 (1H, m), 6.60 (1H, d, $J=15.4Hz$), 7.12-7.86 (17H, m), 8.57 (1H, d, $J=4.4Hz$).

Working Example 80 (Production of Compound 80)

In THF (10ml) was dissolved (E)-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the mixture was added 70% mCPBA (152mg). The mixture was stirred at room temperature for 6 hours, and to the solution were added saturated sodium thiosulfate solution (10ml) and saturated potassium carbonate (10ml). The mixture was stirred at room temperature for 30 minutes and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-methanol to give (E)-N-[4-[hydroxy(1-oxido-2-pyridyl)methyl]phenyl]-3-(4-methylphenyl)cinnamamide (Compound 80) (123mg) as colorless crystals.

mp 165-167°C

Elemental Analysis for $C_{22}H_{26}N_2O$

Calcd: C, 77.04; H, 5.54; N, 6.42.

Found: C, 76.85; H, 5.55; N, 6.42.

IR (KBr) cm^{-1} : 3288, 1668, 1628, 1601, 1539, 1516, 1433, 1412,

5 1340, 1184, 791, 768

1H NMR (200MHz, $CDCl_3$) δ : 2.40 (3H, s), 6.05 (1H, d, $J=4.4Hz$),
6.37 (1H, d, $J=4.4Hz$), 6.65 (1H, d, $J=15.8Hz$), 6.99-7.06
(1H, m), 7.20-7.31 (4H, m), 7.36-7.87 (12H, m), 8.20-8.26
(1H, m).

10 Working Example 81 (Production of Compound 81)

To 3-phenylcinnamic acid (0.62g) were added thionyl
chloride (5ml) and dimethylformamide (catalytic amount),
and the mixture was refluxed for 4 hours. The solvent was
evaporated, and the residue was dissolved in tetrahydro-
15 furan. The mixture was dropwise added to a suspension of
1-(4-aminobenzyl)piperidine (0.5g) and diisopropylethyl-
amine (1.2ml) in tetrahydrofuran (5ml) under ice-cooling.
Under nitrogen atmosphere, the mixture was stirred at room
temperature over night. The solvent was evaporated, and to
20 the residue was added water. The mixture was extracted with
ethyl acetate. The organic layer was washed with water and
saturated sodium chloride solution, and dried with anhydrous
magnesium sulfate. Under reduced pressure, the solvent was
evaporated, and the residue was purified with silica gel
25 column (methanol/triethylamine/ethyl acetate). The
resulting crude crystals was recrystallized from ethyl
acetate-hexane to give 1-(4-(3-phenylcinnamoylamino)-
benzyl)piperidine (Compound 81) (0.45g) as pale yellow
crystals.

30 mp 159-160°C.

1H -NMR (δ ppm, $CDCl_3$): 1.37-1.48 (2H, m), 1.49-1.63 (4H, m),
2.34-2.42 (4H, m), 3.45 (2H, s), 6.62 (1H, d, $J=15.4Hz$),
7.23-7.63 (13H, m), 7.76 (1H, s), 7.83 (1H, d, $J=15.4Hz$).
IR (KBr) ν : 2934, 1659, 1624 cm^{-1} .

35 Anal. for $C_{22}H_{26}N_2O \cdot 0.5H_2O$:

Calcd. C, 79.97; H, 7.21; N, 6.91.

Found C,81.09; H,7.02; N,6.94.

Working Example 82 (Production of Compound 82)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g) and sodium phenyl sulfide (0.05g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-(4-(phenylthiomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 82) (0.13g) as colorless crystals. mp 176-177°C.

¹H-NMR (δ ppm, CDCl₃): 2.39 (3H, s), 3.07 (2H, t, J=4.5Hz), 4.10 (2H, s), 4.35 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.2Hz), 7.18-7.33 (9H, m), 7.43-7.53 (6H, m), 7.58 (1H, s).

IR(KBr) ν: 1652, 1515cm⁻¹.

Anal. for C₂₁H₂₁NO₂S:

Calcd. C,77.96; H,5.70; N,2.93.

Found C,77.72; H,5.57; N,3.07.

Working Example 83 (Production of Compound 83)

A suspension of 1-(4-(3-bromocinnamoylamino)-benzyl)piperidine (0.4g), 4-fluorophenyl borate (0.14g), 1M potassium carbonate (2ml) and ethanol (1ml) in toluene (5ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the suspension was added tetrakis(triphenylphosphine)palladium (0.05g), and the mixture was refluxed over night. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate)

to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 1-(4-(3-(4-fluoro-phenyl)-cinnamoylamino)benzyl)piperidine (Compound 83) (0.35g) as colorless crystals.

5 mp 166-167°C.

¹H-NMR(δ ppm, CDCl₃): 1.38-1.50 (2H, m), 1.52-1.65 (4H, m), 2.34-2.39 (4H, m), 3.45 (2H, s), 6.61 (1H, d, J=15.4Hz), 7.10-7.19 (2H, m), 7.30 (2H, d, J=8.0Hz), 7.40-7.58 (8H, m), 7.68 (1H, s), 7.81 (1H, d, J=15.4Hz).

10 IR(KBr) ν: 3262, 2936, 1663cm⁻¹.

Anal. for C₂₇H₂₇FN₂O·0.2H₂O:

Calcd. C, 77.56; H, 6.61; N, 6.70.

Found C, 77.72; H, 6.49; N, 6.79.

Working Example 84 (Production of Compound 84)

15 A suspension of 1-(4-(3-bromocinnamoylamino)-benzyl)piperidine (0.4g), 4-methoxyphenyl borate (0.14g), 1M potassium carbonate (2ml) and ethanol (1ml) in toluene (5ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the suspension was added

20 tetrakis(triphenylphosphine)palladium (0.05g), and the mixture was refluxed over night. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the

25 solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 1-(4-(3-(4-methoxyphenyl)-cinnamoylamino)benzyl)piperidine (Compound 84) (0.38g) as

30 colorless crystals.

mp 150-151°C.

¹H-NMR(δ ppm, CDCl₃): 1.38-1.50 (2H, m), 1.51-1.62 (4H, m), 2.35-2.40 (4H, m), 3.46 (2H, s), 3.87 (3H, s), 6.61 (1H, d, J=15.4Hz), 7.00 (2H, d, J=9.0Hz), 7.29-7.36 (3H, m),

35 7.43-7.58 (7H, m), 7.71 (1H, s), 7.82 (1H, d, J=15.4Hz).

IR(KBr) ν: 3264, 2936, 1663cm⁻¹.

Anal. for $C_{28}H_{30}N_2O_2$:

Calcd. C, 78.84; H, 7.09; N, 6.57.

Found C, 79.07; H, 7.12; N, 6.69.

Working Example 85 (Production of Compound 85)

- 5 A solution of 1-(4-(3-phenylcinnamoylamino)-benzyl)piperidine (0.32g) and methyl iodide (0.15ml) in dimethylformamide (5ml) was stirred over night under nitrogen atmosphere at room temperature. The solvent was evaporated, and to the residue was added ethyl acetate.
- 10 Precipitated crude crystal was filtered, which were recrystallized from ethanol to give 1-methyl-1-(4-(3-phenylcinnamoylamino)-benzyl)piperidinium iodide (Compound 85) (0.26g) as colorless crystals.
- mp 194-195°C.

- 15 $^1\text{H-NMR}$ (δ ppm, DMSO- d_6): 1.45-1.65 (2H, m), 1.75-1.95 (4H, m), 2.92 (3H, s), 3.24-3.28 (4H, m), 4.54 (2H, s), 6.97 (1H, d, $J=15.8\text{Hz}$), 7.41-7.93 (14H, m), 10.44 (1H, s).
- IR(KBr) ν : 3241, 1682 cm^{-1} .

Anal. for $C_{28}H_{31}IN_2O$:

- 20 Calcd. C, 62.46; H, 5.80; N, 5.20.

Found C, 62.19; H, 5.74; N, 5.10.

Working Example 86 (Production of Compound 86)

- A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g)
- 25 and sodium benzyl sulfide (0.055g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride
- 30 solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(benzylthiomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-
- 35 carboxamide (Compound 86) (0.17g) as colorless crystals.
- mp 145-146°C.

¹H-NMR (δ ppm, CDCl₃): 2.39 (3H, s), 3.07 (2H, t, J=4.7Hz), 3.59 (2H, s), 3.60 (2H, s), 4.35 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.0Hz), 7.22-7.32 (9H, m), 7.43-7.57 (6H, m), 7.61 (1H, s).

5 IR(KBr) ν: 3028, 1646, 1515cm⁻¹.

Anal. for C₁₃H₁₁NO₂S·0.5H₂O:

Calcd. C, 76.77; H, 6.04; N, 2.80.

Found C, 77.07; H, 5.96; N, 2.95.

Working Example 87 (Production of Compound 87)

10 A solution of Compound 83 (0.25g) and methyl iodide (0.2ml) in dimethylformamide (5ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol

15 to give 1-methyl-1-(4-(3-(4-fluorophenyl)cinnamoylamino)-benzyl)piperidinium iodide (Compound 87) (0.27g) as pale brown crystals.

mp 204-205°C.

¹H-NMR (δ ppm, DMSO-d₆): 1.42-1.75 (2H, m), 1.78-1.95 (4H, m), 20 2.91 (3H, s), 3.22-3.32 (4H, m), 4.52 (2H, s), 6.95 (1H, d, J=15.8 Hz), 7.29-7.38 (2H, m), 7.48-7.91 (11H, m), 10.44 (1H, s).

IR(KBr) ν: 3237, 1682cm⁻¹.

Anal. for C₂₆H₂₀FIN₂O·0.5H₂O:

25 Calcd. C, 59.47; H, 5.53; N, 4.95.

Found C, 59.49; H, 5.35; N, 4.98.

Working Example 88 (Production of Compound 88)

A solution of 1-(4-(3-(4-methoxyphenyl)cinnamoylamino)benzyl)piperidine (0.32g) and methyl iodide (0.2ml)

30 in dimethylformamide (5ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-hexane to give 1-methyl-1-(4-(3-(4-methoxyphenyl)cinnamoylamino)-

35 benzyl)piperidinium iodide (Compound 88) (0.33g) as pale brown crystals.

mp 208-209°C.

¹H-NMR(δ ppm, DMSO-d₆): 1.45-1.68 (2H, m), 1.78-1.95 (4H, m),
2.91 (3H, s), 3.24-3.34 (4H, m), 3.82 (3H, s), 4.53 (2H,
s), 6.95 (1H, d, J=15.8Hz), 7.06 (2H, d, J=8.6Hz), 7.43-7.57
5 (4H, m), 7.61-7.74 (4H, m), 7.84 (2H, d, J=8.6Hz), 7.88 (1H,
s), 10.45 (1H, s).

IR(KBr) ν : 3243, 1682cm⁻¹.

Anal. for C₂₉H₃₃IN₂O₂:

Calcd. C, 61.27; H, 5.85; N, 4.93.

10 Found C, 60.87; H, 5.83; N, 4.88.

Working Example 89 (Production of Compound 89)

To 3,4-dihydro-7-phenylnaphthalene-2-carboxylic acid
(0.25g) were added thionyl chloride (5ml) and
dimethylformamide (catalytic amount), and the mixture was
15 refluxed for 3 hours. The solvent was evaporated, and the
residue was dissolved in tetrahydrofuran. The mixture was
dropwise added to a suspension of 2-(4-aminobenzyl)-
1,3-dimethyl-1,3,2-diazaphosphorinane-2-oxide (0.25g) and
diisopropylethylamine (0.5ml) in tetrahydrofuran (10ml),
20 under ice-cooling. Under nitrogen atmosphere, the mixture
was stirred at room temperature over night. The solvent was
evaporated, and to the residue was added water. The mixture
was extracted with ethyl acetate. The organic layer was
washed with water and saturated sodium chloride solution,
25 and dried with anhydrous magnesium sulfate. Under reduced
pressure, the solvent was evaporated. Precipitated crude
crystal was recrystallized from ethanol-hexane to give
2-(4-(3,4-dihydro-7-phenyl-naphthalene-2-carbonyl-
amino)benzyl)-1,3-dimethyl-1,3,2-diazaphosphorinane-2-
30 oxide (Compound 89) (0.35g) as colorless crystals.

mp 249-250°C.

¹H-NMR(δ ppm, CDCl₃): 1.10-1.30 (1H, m), 1.65-1.85 (1H, m),
2.65 (3H, s), 2.69 (3H, s), 2.73-3.07 (8H, m), 3.17 (2H,
d, J=17.4Hz), 7.18 (2H, dd, J=2.6, 8.8Hz), 7.29-7.60 (11H,
35 m), 7.70 (1H, s).

IR(KBr) ν : 3283, 2940, 2886, 2832, 1655cm⁻¹.

Anal. for $C_{29}H_{32}N_2O_2P \cdot 0.2H_2O$:

Calcd. C, 71.21; H, 6.68; N, 8.59.

Found C, 71.12; H, 6.57; N, 8.52.

Working Example 90 (Production of Compound 90)

- 5 To 3,4-dihydro-7-phenylnaphthalene-2-carboxylic acid (0.35g) were added thionyl chloride (10ml) and dimethylformamide (catalytic amount), and the mixture was refluxed for 2.5 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was
- 10 dropwise added a suspension of 2-(4-aminobenzyl)-1,3-dimethyl-1,3,2-diazaphosphorane-2-oxide (0.33g) and diisopropylethylamine (0.75ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was
- 15 evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated. Precipitated crude
- 20 crystal was recrystallized from ethanol-hexane to give 2-(4-(3,4-dihydro-7-phenyl-naphthalene-2-carbonyl-amino)benzyl)-1,3-dimethyl-1,3,2-diaza-phosphorane-2-oxide (Compound 90) (0.24g) as colorless crystals. mp 212-213°C.

- 25 1H -NMR (δ ppm, $CDCl_3$): 2.61 (3H, s), 2.65-2.76 (2H, m), 2.66 (3H, s), 2.94-3.07 (2H, m), 3.22 (2H, d, $J=18.6$ Hz), 7.19 (2H, dd, $J=2.6, 8.6$ Hz), 7.29-7.60 (11H, m), 7.72 (1H, s). IR(KBr) ν : 3254, 2928, 2897, 1655 cm^{-1} .

Anal. for $C_{28}H_{30}N_2O_2P \cdot 0.5H_2O$:

- 30 Calcd. C, 69.98; H, 6.50; N, 8.74.

Found C, 70.27; H, 6.32; N, 8.53.

Working Example 91 (Production of Compound 91)

- To a solution of 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.25g) in
- 35 dichloromethane (5ml) were added oxalyl chloride (0.4ml) and dimethylformamide (catalytic amount) under ice-cooling,

and the mixture was stirred at 40°C for 1 hour. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 1-(4-aminobenzyl)piperidine (0.17g) and diisopropylethylamine (0.5ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with dichloromethane, and the organic layer was washed with water and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and precipitated crude crystal was recrystallized from dichloromethane-hexane to give 2-(4-methylphenyl)-N-(4-piperidinomethylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 91) (0.36g) as colorless crystals.
mp 192-193°C.

¹H-NMR (δ ppm, CDCl₃): 1.38-1.50 (2H, m), 1.50-1.63 (4H, m), 2.13-2.22 (2H, m), 2.35-2.39 (4H, m), 2.40 (3H, s), 2.72 (2H, t, J=6.4Hz), 2.85-2.91 (2H, m), 3.46 (2H, s), 7.21-7.33 (5H, m), 7.41-7.57 (6H, m), 7.63 (1H, s).

IR(KBr) ν: 3352, 2932, 1647cm⁻¹.

Anal. for C₃₁H₃₄N₂O·0.2H₂O:

Calcd. C, 81.97; H, 7.63; N, 6.17.

Found C, 81.88; H, 7.52; N, 6.22.

Working Example 92 (Production of Compound 92)

A solution of 2-(4-methylphenyl)-N-(4-piperidinomethylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.26g) and methyl iodide (0.15ml) in dimethylformamide (15ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-ethyl acetate to give 1-(N-(2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carbonyl)-4-aminobenzyl)-1-methylpiperidinium iodide (Compound 92) (0.3g) as colorless

crystals.

mp 220-221°C (dec.).

¹H-NMR (δ ppm, DMSO-d₆): 1.45-1.65 (2H, m), 1.80-1.94 (4H, m),
1.99-2.09 (2H, m), 2.35 (3H, s), 2.64 (2H, t, J=6.1Hz),
5 2.83-2.88 (2H, m), 2.91 (3H, s), 3.23-3.29 (4H, m), 4.53
(2H, s), 7.26-7.38 (4H, m), 7.48-7.68 (6H, m), 7.87 (2H,
d, J=8.6Hz), 10.23 (1H, s).

IR(KBr) ν: 3285, 2946, 1651cm⁻¹.

Anal. for C₂₂H₂₇IN₂O·0.5H₂O:

10 Calcd. C, 63.89; H, 6.37; N, 4.66.

Found C, 63.94; H, 6.33; N, 4.60.

Working Example 93 (Production of Compound 93)

To a solution of 7-(4-methylphenyl)-N-(4-hydroxy-
methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide
15 (0.2g), triethylamine (0.21ml) and dimethylaminopyridine
(catalytic amount) in tetrahydrofuran (10ml) was dropwise
added methane-sulfonylchloride (0.06ml) under ice-cooling,
and the mixture was stirred for 10 minutes. To the mixture
was added piperidine (0.15ml), and the mixture was stirred
20 at room temperature for 2 hours. The solvent was evaporated,
and to the residue was added water. The mixture was
extracted with ethyl acetate. The organic layer was washed
with water and saturated sodium chloride solution, and dried
with anhydrous magnesium sulfate. Under reduced pressure,
25 the solvent was evaporated, and the residue was purified
with silica gel column (methanol/triethylamine/ethyl
acetate) to give crude crystals, which were recrystallized
from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-
(4-piperidinomethylphenyl)-2,3-dihydro-1-benzothiepine-
30 4-carboxamide (Compound 93) (0.19g) as colorless crystals.
mp 203-204°C.

¹H-NMR (δ ppm, CDCl₃): 1.35-1.50 (2H, m), 1.55-1.63 (4H, m),
2.38-2.40 (4H, m), 2.40 (3H, s), 3.08 (2H, t, J=5.7Hz), 3.29
(2H, t, J=5.7Hz), 3.47 (2H, s), 7.24-7.46 (7H, m), 7.50-7.58
35 (5H, m), 7.68 (1H, s).

IR(KBr) ν: 2934, 1651cm⁻¹.

Anal. for $C_{30}H_{32}N_2OS \cdot 0.2H_2O$:

Calcd. C, 76.30; H, 6.92; N, 5.93.

Found C, 76.27; H, 6.77; N, 6.06.

Working Example 94 (Production of Compound 94)

- 5 A solution of 7-(4-methylphenyl)-N-(4-piperidino-methyl-phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (0.08g) and methyl iodide (0.013ml) in dimethylformamide (20ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue
10 was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-hexane to give 1-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carbonyl)-4-aminobenzyl)-1-methyl-piperidinium iodide (Compound 94) (0.077g) as colorless
15 crystals.

mp 196-197°C.

- 1H -NMR (δ ppm, DMSO- d_6): 1.45-1.65 (2H, m), 1.80-1.95 (4H, m), 2.35 (3H, s), 2.91 (3H, s), 2.99-3.05 (2H, m), 3.15-3.29 (6H, m), 4.53 (2H, s), 7.29 (2H, d, $J=8.2$ Hz), 7.46-7.63 (7H, m), 7.82-7.89 (3H, m), 10.34 (1H, s).
20

IR(KBr) ν : 3284, 2947, 1652 cm^{-1} .

Anal. for $C_{31}H_{35}IN_2OS \cdot 0.5H_2O$:

Calcd. C, 60.09; H, 5.86; N, 4.52.

Found C, 60.03; H, 5.57; N, 4.44.

- 25 Working Example 95 (Production of Compound 95)

- To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (1.0g) in dichloromethane (30ml) were added oxalyl chloride (0.93ml) and dimethylformamide (catalytic amount), under ice-cooling, and the
30 mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 1-(4-amino-benzyl)piperidine (0.75g) and triethylamine (1.5ml) in tetra-hydrofuran (50ml), under
35 ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was

- evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals which were recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-(4-((piperidinomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 95) (1.45g) as colorless crystals.
- mp 188-189°C.
- ¹H-NMR(δ ppm, CDCl₃): 1.40-1.47 (2H, m), 1.52-1.60 (4H, m), 2.34-2.39 (4H, m), 2.39 (3H, s), 3.07 (2H, t, J=4.4Hz), 3.46 (2H, s), 4.36 (2H, t, J=4.4Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.33 (5H, m), 7.43-7.58 (6H, m).
- IR(KBr) ν: 2935, 1652cm⁻¹.
- Anal. for C₃₀H₃₂N₂O₂:
- Calcd. C, 79.61; H, 7.13; N, 6.19.
- Found C, 79.53; H, 6.91; N, 6.22.
- Working Example 96 (Production of Compound 96)
- A solution of 7-(4-methylphenyl)-N-(4-((piperidinomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (1.4g) and methyl iodide (0.58ml) in dimethylformamide (50ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-ethyl acetate to give 1-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)-1-methylpiperidinium iodide (Compound 96) (1.6g) as colorless crystals.
- mp 227-228°C(dec.).
- ¹H-NMR(δ ppm, DMSO-d₆): 1.45-1.70 (2H, m), 1.70-1.95 (4H, m), 2.34 (3H, s), 2.91 (3H, s), 3.00 (2H, br), 3.24-3.34 (4H, m), 4.31 (2H, br), 4.53 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=8.0Hz), 7.36 (1H, s), 7.48-7.59 (5H, m), 7.75 (1H, s), 7.86 (2H, d, J=8.8Hz), 10.19 (1H, s).
- IR(KBr) ν: 3289, 2938, 1649cm⁻¹.

Anal. for $C_{31}H_{33}IN_2O_2$:

Calcd. C, 62.63; H, 5.93; N, 4.71.

Found C, 62.43; H, 5.91; N, 4.52.

Working Example 97 (Production of Compound 97)

5 A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g) and 1-methylpiperidine (0.14ml) in dimethylformamide (15ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-diethylether to give 1-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)-1-methylpiperidinium chloride (Compound 97) (0.15g) as colorless crystals.
15 mp 231-232°C.

1H -NMR (δ ppm, DMSO- d_6): 1.45-1.65 (2H, m), 1.80-1.95 (4H, m), 2.34 (3H, s), 2.91 (3H, s), 2.97-3.05 (2H, m), 3.23-3.30 (4H, m), 4.25-4.35 (2H, m), 4.53 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=8.4Hz), 7.38 (1H, s), 7.48-7.59 (5H, m), 7.75 (1H, s), 7.86 (2H, d, J=8.8Hz), 10.23 (1H, s).

IR(KBr) ν : 3227, 2969, 1665 cm^{-1} .

Anal. for $C_{31}H_{33}ClN_2O_2 \cdot 0.5H_2O$:

Calcd. C, 72.71; H, 7.09; N, 5.47.

25 Found C, 72.85; H, 6.93; N, 5.48.

Working Example 98 (Production of Compound 98)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.18g) and 1-ethylpiperidine (0.31ml) in dimethylformamide (5ml) were stirred at 50°C overnight. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-ethyl acetate to give 1-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-amino-benzyl)-1-ethylpiperidinium chloride (Compound 98) (0.17g) as colorless crystals.
35

mp 209-210°C.

¹H-NMR(δ ppm, DMSO-d₆): 1.34 (3H, t, J=6.9Hz), 1.38-1.66 (2H, m), 1.80-1.99 (4H, m), 2.34 (3H, s), 3.00 (2H, t, J=4.2Hz), 3.13-3.31 (6H, m), 4.30 (2H, t, J=4.2Hz), 4.50 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=8.0Hz), 7.39 (1H, s), 7.46-7.59 (5H, m), 7.76 (1H, d, J=2.2Hz), 7.87 (2H, d, J=8.8Hz), 10.24 (1H, s).

IR(KBr) ν: 3202, 2946, 1645cm⁻¹.

Anal. for C₂₂H₂₁ClN₂O₂·0.3H₂O:

10 Calcd. C, 73.56; H, 7.25; N, 5.36.

Found C, 73.59; H, 7.26; N, 5.32.

Working Example 99 (Production of Compound 99)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloro-
15 methane (5ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a
20 solution of 1-(2-(4-aminophenyl)ethyl)piperidine (0.11g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture
25 was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals which were recrystallized from ethyl acetate-hexane to give
30 N-(4-(2-piperidinoethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 99) (0.19g) as colorless crystals.

mp 201-202°C.

¹H-NMR(δ ppm, CDCl₃): 1.45-1.48 (2H, m), 1.50-1.65 (4H, m), 2.39 (3H, s), 2.47-2.58 (6H, m), 2.76-2.84 (2H, m), 3.07 (2H, t, J=4.4Hz), 4.36 (2H, t, J=4.4Hz), 7.05 (1H, d,

J=8.0Hz), 7.17-7.26 (4H, m), 7.43-7.51 (7H, m).

IR(KBr) ν : 2933, 1652cm⁻¹.

Anal. for C₂₁H₂₃N₂O₂:

Calcd. C, 79.79; H, 7.34; N, 6.00.

5 Found C, 79.63; H, 7.42; N, 6.07.

Working Example 100 (Production of Compound 100)

A solution of N-(4-(2-piperidinoethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.09g) and methyl iodide (0.06ml) in
10 dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-hexane to give N-((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-
15 carbonyl)-2-(4-aminophenyl)ethyl)-N-methylpiperidinium iodide (Compound 100) (0.12g) as pale yellow crystals. mp 168-169°C.

¹H-NMR(δ ppm, CDCl₃): 1.65-1.95 (6H, m), 2.35 (3H, s),
2.95-3.05 (4H, m), 3.25 (3H, s), 3.61-3.85 (6H, m), 4.29
20 (2H, t, J=4.2Hz), 7.01 (1H, d, J=8.4Hz), 7.17-7.26 (4H, m),
7.40-7.50 (4H, m), 7.58 (2H, d, J=8.4Hz), 7.70 (1H, d,
J=2.2Hz), 8.49 (1H, br).

IR(KBr) ν : 2949, 1656cm⁻¹.

Anal. for C₃₂H₃₇IN₂O₂·0.5H₂O:

25 Calcd. C, 62.24; H, 6.20; N, 4.54.

Found C, 61.92; H, 6.17; N, 4.57.

Working Example 101 (Production of Compound 101)

To a suspension of 7-(4-methylphenyl)-2-phenyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in
30 dichloro-methane (10ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a
35 solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)amino-methyl)aniline (0.06g) and triethylamine (0.12ml) in

tetrahydrofuran (5ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate.

- 5 The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were
- 10 recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-2-phenyl-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 101) (0.11g) as colorless crystals. mp 178-179°C.

- 15 ¹H-NMR(δ ppm, CDCl₃): 1.63-1.74 (4H, m), 2.20 (3H, s), 2.40 (3H, s), 2.56-2.66 (1H, m), 3.15-3.43 (4H, m), 3.56 (2H, s), 4.01-4.05 (2H, m), 5.09 (1H, dd, J=2.2, 8.4Hz), 7.10 (1H, d, J=8.4Hz), 7.17-7.57 (16H, m).
IR(KBr) ν: 2949, 2844, 1652cm⁻¹.

- 20 Anal. for C₃₇H₃₈N₂O₃:
Calcd. C, 79.54; H, 6.86; N, 5.01.
Found C, 79.28; H, 6.96; N, 4.97.

Working Example 102 (Production of Compound 102)

- To a suspension of 7-(4-methylphenyl)-2-phenyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in
- 25 dichloro-methane (10ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved
- 30 in tetrahydrofuran. The mixture was dropwise added to a solution of 1-(4-amino-benzyl)piperidine (0.06g) and triethylamine (0.12ml) in tetrahydrofuran (5ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was
- 35 evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was

- washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-2-phenyl-N-(4-(piperidinomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 102) (0.12g) as colorless crystals. mp 210-211°C.
- ¹H-NMR(δ ppm, CDCl₃): 1.40-1.47 (2H, m), 1.52-1.62 (4H, m), 2.34-2.40 (4H, m), 2.40 (3H, s), 3.23-3.31 (2H, m), 3.45 (2H, s), 5.09 (1H, dd, J=2.0, 8.8Hz), 7.10 (1H, d, J=8.4Hz), 7.23-7.56 (16H, m).
IR(KBr) ν: 2935, 1652cm⁻¹.
- Anal. for C₃₆H₃₆N₂O₂:
Calcd. C, 81.79; H, 6.86; N, 5.30.
Found C, 81.45; H, 6.82; N, 5.28.
- Working Example 103 (Production of Compound 103)
- A solution of 7-(4-methylphenyl)-2-phenyl-N-(4-(piperidinomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.08g) and methyl iodide (0.05ml) in dimethylformamide (15ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-ethyl acetate to give 1-(N-(7-(4-methylphenyl)-2-phenyl-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)-1-methylpiperidinium iodide (Compound 103) (0.057g) as colorless crystals.
- mp 232-233°C(dec.).
¹H-NMR(δ ppm, DMSO-d₆): 1.45-1.70 (2H, m), 1.75-1.95 (4H, m), 2.35 (3H, s), 2.91 (3H, s), 3.25-3.44 (6H, m), 4.53 (2H, s), 5.12 (1H, t, J=5.0Hz), 7.09 (1H, d, J=8.4Hz), 7.28 (2H, d, J=8.2Hz), 7.37-7.61 (11H, m), 7.81-7.87 (3H, m), 10.20 (1H, s).
IR(KBr) ν: 2949, 1650cm⁻¹.

Anal. for $C_{17}H_{18}IN_2O_3 \cdot 0.2H_2O$:

Calcd. C, 65.91; H, 5.89; N, 4.15.

Found C, 65.80; H, 5.84; N, 4.17.

Working Example 104 (Production of Compound 104)

- 5 To a suspension of 7-(4-methylphenyl)-2-methyl-
2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in
dichloro-methane (5ml) were added oxalyl chloride (0.1ml)
and dimethylformamide (catalytic amount) under ice-cooling,
and the mixture was stirred at room temperature for 2 hours.
- 10 The solvent was evaporated, and the residue was dissolved
in tetrahydrofuran. The mixture was dropwise added to a
solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)amino-
methyl)aniline (0.08g) and triethylamine (0.14ml) in
tetrahydrofuran (5ml), under ice-cooling. Under nitrogen
- 15 atmosphere, the mixture was stirred at room temperature over
night. The solvent was evaporated, and to the residue was
added water. The mixture was extracted with ethyl acetate.
The organic layer was washed with water and saturated sodium
chloride solution, and dried with anhydrous magnesium
- 20 sulfate. Under reduced pressure, the solvent was
evaporated to give crude crystals, which were recrystallized
from ethyl acetate-hexane to give 7-(4-methylphenyl)-2-
methyl-N-(4-((N-tetrahydropyran-4-yl-N-
methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-
25 carboxamide (Compound 104) (0.12g) as colorless crystals.
mp 170-171°C.
- 1H -NMR (δ ppm, $CDCl_3$): 1.54 (3H, d, $J=6.4Hz$), 1.60-1.78 (4H,
m), 2.22 (3H, s), 2.39 (3H, s), 2.63-2.68 (1H, m), 2.85 (1H,
ddd, $J=2.6, 9.2, 17.6Hz$), 3.14 (1H, d, $J=17.6Hz$), 3.37 (2H,
30 dt, $J=2.8, 11.3Hz$), 3.58 (2H, s), 4.01-4.07 (2H, m),
4.24-4.30 (1H, m), 7.05 (1H, d, $J=8.4Hz$), 7.22-7.34 (4H,
m), 7.43-7.56 (7H, m).
- IR(KBr) ν : 2951, 2845, 1651 cm^{-1} .
- Anal. for $C_{22}H_{26}N_2O_3$:
- 35 Calcd. C, 77.39; H, 7.31; N, 5.64.
Found C, 77.21; H, 7.43; N, 5.51.

Working Example 105 (Production of Compound 105)

To a suspension of 7-(4-methylphenyl)-2-methyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in dichloro-methane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 1-(4-aminobenzyl)piperidine (0.07g) and triethylamine (0.14ml) in tetrahydrofuran (5ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-2-methyl-N-(4-(piperidinomethyl)-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 105) (0.12g) as colorless crystals. mp 175-176°C.

¹H-NMR(δ ppm, CDCl₃): 1.40-1.45 (2H, m), 1.54 (3H, d, J=6.2Hz), 1.53-1.61 (4H, m), 2.30-2.40 (4H, m), 2.39 (3H, s), 2.85 (1H, ddd, J=2.6, 8.8, 18.0Hz), 3.14 (1H, d, J=18.0Hz), 3.47 (2H, s), 4.23-4.30 (1H, m), 7.05 (1H, d, J=8.8Hz), 7.16-7.36 (4H, m), 7.43-7.55 (7H, m)..

IR(KBr) ν: 2936, 1651cm⁻¹.

Anal. for C₃₁H₃₄N₂O₂:

Calcd. C, 79.79; H, 7.34; N, 6.00.

Found C, 79.53; H, 7.35; N, 5.82.

Working Example 106 (Production of Compound 106)

To a solution of N-(4-(cyclohexylthiomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.19g) in dichloro-methane (5ml) was added 70% m-chloroperbenzoic acid (0.097g)

under ice-cooling, and the mixture was stirred for 10 minutes. To the mixture was added sodium thiosulfate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/dichloromethane) to give crude crystals, which were recrystallized from ethanol to give N-(4-

5 (cyclohexylsulfinylmethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 106) (0.048g) as colorless crystals.

mp 257-258°C(dec.).
¹H-NMR(δ ppm, CDCl₃): 1.19-1.69 (6H, m), 1.81-1.85 (3H, m),
15 2.01-2.08 (1H, m), 2.40 (3H, s), 2.40-2.49 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.90 (2H, dd, J=13.2, 24.2Hz), 4.35 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.6Hz), 7.23-7.28 (4H, m), 7.44-7.54 (4H, m), 7.60 (2H, d, J=8.4Hz), 8.07 (1H, s).
IR(KBr) ν: 2930, 2853, 1659cm⁻¹.

20 Anal. for C₂₁H₂₃NO₃S·0.3H₂O:
Calcd. C, 73.72; H, 6.71; N, 2.77.
Found C, 73.66; H, 6.70; N, 2.80.

Working Example 107 (Production of Compound 107)

To a solution of N-(4-(cyclohexylsulfinylmethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.13g) in chloroform (45ml) was added 70% m-chloroperbenzoic acid (mCPBA) (0.097g) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added sodium thiosulfate solution, and the mixture was washed with sodium hydrogen carbonate solution and water, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethanol-hexane to give N-(4-(cyclohexylsulfonyl-

25 methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 107) (0.11g) as

30

35

colorless crystals.

mp 250-251°C.

¹H-NMR(δ ppm, CDCl₃): 1.18-1.26 (4H, m), 1.52-1.71 (2H, m),
1.87-1.94 (2H, m), 2.09-2.17 (2H, m), 2.40 (3H, s), 2.65-2.83
5 (1H, m), 3.08 (2H, t, J=4.6Hz), 4.18 (2H, s), 4.37 (2H, t,
J=4.6Hz), 7.07 (1H, d, J=8.4Hz), 7.23-7.27 (2H, m),
7.38-7.53 (6H, m), 7.65 (2H, d, J=8.6Hz), 7.70 (1H, s).
IR(KBr) ν: 2932, 2857, 1667cm⁻¹.

Anal. for C₃₁H₃₃NO₄S·0.2H₂O:

10 Calcd. C, 71.70; H, 6.48; N, 2.70.

Found C, 71.70; H, 6.54; N, 2.79.

Working Example 108 (Production of Compound 108)

To a solution of 7-(4-methylphenyl)-N-(4-(phenyl-
thiomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-
15 carboxamide (0.1g) in dichloromethane (30ml) was added 70%
m-chloroperbenzoic acid (0.046g) at the temperature ranging
from -20 to -10°C, and the mixture was stirred for 30 minutes.
To the mixture was added sodium thiosulfate solution, and
the mixture was concentrated and extracted with ethyl
20 acetate. The organic layer was washed with sodium hydrogen
carbonate solution, water and saturated sodium chloride
solution, and dried with anhydrous magnesium sulfate.
Under reduced pressure, the solvent was evaporated to give
crude crystals, which were recrystallized from ethyl
25 acetate-hexane to give 7-(4-methylphenyl)-N-(4-
(phenylsulfinylmethyl)phenyl)-2,3-dihydro-1-
benzoxepine-4-carboxamide (Compound 108) (0.11g) as
colorless crystals.

mp 127-128°C.

30 ¹H-NMR(δ ppm, CDCl₃): 2.39 (3H, s), 3.06 (2H, t, J=4.6Hz),
4.01 (2H, s), 4.34 (2H, t, J=4.6Hz), 6.95 (2H, d, J=8.8Hz),
7.05 (1H, d, J=8.0Hz), 7.22-7.26 (3H, m), 7.37-7.53 (10H,
m), 7.85 (1H, s).

IR(KBr) ν: 3026, 2925, 1652cm⁻¹.

35 Anal. for C₃₁H₂₇NO₄S:

Calcd. C, 75.43; H, 5.51; N, 2.84.

chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/triethylamine=20/1) and recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-[4-(4-methyl-1-piperazinylmethyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 40) (105mg) as colorless crystals. mp 174-175°C

Elemental Analysis for $C_{26}H_{27}N_3O$

10 Calcd: C, 79.79; H, 7.37; N, 9.30.

Found: C, 79.43; H, 7.41; N, 9.28.

IR (KBr) cm^{-1} : 3327, 2941, 2794, 1643, 1524, 1315, 1163, 1011, 808

1H NMR (200MHz, $CDCl_3$) δ : 2.29 (3H, s), 2.35-2.60 (8H, m), 2.40 (3H, s), 2.65-2.78 (2H, m), 2.90-3.02 (2H, m), 3.48 (2H, s), 7.20-7.35 (6H, m), 7.39-7.63 (7H, m).

Working Example 41 (Production of Compound 41)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the solution were added 1-(2-methoxyphenyl)piperazine (97mg) and potassium carbonate (268mg). The mixture was stirred at room temperature for 13 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give N-[4-[1-(2-methoxyphenyl)-4-piperazinylmethyl]phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 41) (142mg) as colorless crystals. mp 202-205°C

Elemental Analysis for $C_{26}H_{27}N_3O_2$

Calcd: C, 79.53; H, 6.86; N, 7.73.

35 Found: C, 79.28; H, 6.68; N, 7.66.

IR (KBr) cm^{-1} : 3350, 2933, 2812, 1649, 1595, 1520, 1500, 1313,

1240, 812, 746

¹H NMR (200MHz, CDCl₃) δ: 2.40 (3H, s), 2.60-2.75 (6H, m),
2.90-3.12 (6H, m), 3.57 (2H, s), 3.86 (3H, s), 6.80-7.03
(4H, m), 7.20-7.28 (3H, m), 7.30-7.38 (3H, m), 7.40-7.51
5 (4H, m), 7.53-7.63 (3H, m).

Working Example 42 (Production of Compound 42)

In THF (7ml) was dissolved N-[4-(chloromethyl)-
phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-
carboxamide (150mg), and to the mixture was added 1-(2-
10 pyrimidyl)piperazine (190mg). The mixture was refluxed for
24 hours. The reaction mixture was cooled to room
temperature, and to the mixture was added 5% sodium hydrogen
carbonate solution (50ml). The mixture was extracted with
ethyl acetate. The organic layer was washed with saturated
15 sodium chloride solution, dried with anhydrous sodium
sulfate, and concentrated under reduced pressure. The
residue was separated and purified with column
chromatography (ethyl acetate) and recrystallized from
ethyl acetate-hexane to give 7-(4-methylphenyl)-N-[4-
20 [1-(2-pyrimidyl)-4-piperazinylmethyl]-phenyl]-3,4-
dihydronaphthalene-2-carboxamide (Compound 42) (166mg) as
colorless crystals.

mp 203-204°C

Elemental Analysis for C₂₃H₂₃N₃O

25 Calcd: C, 76.87; H, 6.45; N, 13.58.

Found: C, 76.77; H, 6.40; N, 13.60.

IR (KBr) cm⁻¹: 3367, 2935, 1649, 1585, 1516, 1448, 1358, 1313,
1255, 984, 808

¹H NMR (200MHz, CDCl₃) δ: 2.40 (3H, s), 2.47-2.54 (4H, m),
30 2.65-2.78 (2H, m), 2.93-3.03 (2H, m), 3.53 (2H, s), 3.79-3.87
(4H, m), 6.47 (1H, t, J=4.8Hz), 7.23-7.28 (3H, m), 7.30-7.38
(3H, m), 7.42-7.52 (4H, m), 7.54-7.62 (3H, m), 8.30 (2H,
d J=4.8Hz).

Working Example 43 (Production of Compound 43)

35 In DMF (3ml) was dissolved N-[4-(chloromethyl)-
phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-

carboxamide (150mg), and to the solution were added 1-benzhydrylpiperazine (127mg) and potassium carbonate (268mg). The mixture was stirred at room temperature for 24 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from acetone-diisopropylether to give N-[4-(4-benzhydryl-1-piperazinyl-methyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 43) (140mg) as colorless crystals.

mp 217-218°C

Elemental Analysis for $C_{27}H_{27}N_3O$

Calcd: C, 83.55; H, 6.84; N, 6.96.

Found: C, 83.25; H, 6.86; N, 7.06.

IR (KBr) cm^{-1} : 3417, 2954, 2812, 1659, 1618, 1520, 1410, 1313, 1007, 810, 706

^1H NMR (200MHz, DMSO- d_6) δ : 2.20-2.65 (13H, m), 2.80-2.93 (2H, m), 3.42 (s, 2H), 4.26 (1H, s), 7.10-7.70 (22H, m), 9.90 (1H, s).

Working Example 44 (Production of Compound 44)

In DMF (3ml) was dissolved N-[4-(chloromethyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the solution were added 1-(2-furoyl)piperazine hydrochloride (109mg) and potassium carbonate (268mg). The mixture was stirred at room temperature for 18 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified with ethyl acetate-diisopropylether to give N-[4-[1-(2-furoyl)-4-piperazinylmethyl]phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 44) (112mg) as colorless amorphous.

IR (KBr) cm^{-1} : 3309, 2920, 1618, 1518, 1489, 1437, 1313, 1184, 1001, 812, 754

Elemental Analysis for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_4$

Calcd: C, 76.81; H, 6.26; N, 7.90.

5 Found: C, 76.60; H, 6.02; N, 7.61.

^1H NMR (200MHz, CDCl_3) δ : 2.40 (3H, s), 2.43-2.55 (4H, m), 2.65-2.78 (2H, m), 2.90-3.03 (2H, m), 3.52 (2H, s), 3.73-3.87 (4H, m), 6.44-6.49 (1H, m), 6.98 (1H, d, $J=3.2\text{Hz}$), 7.20-7.68 (14H, m).

10 Working Example 45 (Production of Compound 45)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the solution were added 1-(3,4,5-trimethoxybenzyl)piperazine (138mg) and potassium carbonate (268mg). The mixture was stirred at room temperature for 48 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give N-[4-[1-(3,4,5-trimethoxybenzyl)-4-piperazinylmethyl]-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 45) (155mg) as pale yellow crystals. mp 143-144°C

25 Elemental Analysis for $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_7$

Calcd: C, 75.82; H, 7.02; N, 6.80.

Found: C, 75.74; H, 6.85; N, 6.75.

30 IR (KBr) cm^{-1} : 3425, 2935, 2806, 1649, 1593, 1520, 1458, 1421, 1313, 1236, 1128, 1009, 810

^1H NMR (200MHz, CDCl_3) δ : 2.40 (3H, s), 2.40-2.55 (8H, m), 2.65-2.77 (2H, m), 2.90-3.03 (2H, m), 3.45 (2H, s), 3.51 (2H, s), 3.84 (3H, s), 3.86 (6H, s), 6.56 (2H, s), 7.20-7.36 (6H, m), 7.40-7.62 (7H, m).

35 Working Example 46 (Production of Compound 46)

In THF (7ml) was dissolved N-[4-(chloromethyl)-

phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 1-(2-hydroxyethyl)piperazine (142 μ l). The mixture was refluxed for 22 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give N-[4-[1-(2-hydroxyethyl)-4-piperazinylmethyl]phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 46) (158mg) as colorless crystals.

mp 185-187°C

Elemental Analysis for $C_{31}H_{35}N_3O_2 \cdot 0.3H_2O$

Calcd: C, 76.45; H, 7.37; N, 8.63.

Found: C, 76.64; H, 7.13; N, 8.35.

IR (KBr) cm^{-1} : 3319, 2937, 2816, 1649, 1597, 1520, 1412, 1317,

812

1H NMR (200MHz, $CDCl_3$) δ : 2.40 (3H, s), 2.43-2.61 (10H, m), 2.65-2.78 (2H, m), 2.92-3.03 (2H, m), 3.50 (2H, s), 3.61 (2H, t, $J=5.5Hz$), 7.21-7.36 (6H, m), 7.40-7.63 (7H, m).

Working Example 47 (Production of Compound 47)

In THF (7ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 3-aminopyridine (109mg). The mixture was refluxed for 45 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=3/1) and recrystallized from ethyl

acetate-hexane to give 7-(4-methylphenyl)-N-[4-[N-(3-pyridyl)aminomethyl]phenyl]-3,4-dihydronaphthalene-2-carboxamide (Compound 47) (14mg) as colorless crystals. mp 212-214°C

5 IR (KBr) cm^{-1} : 3383, 3022, 1655, 1591, 1516, 1412, 1315, 1254, 808, 708

^1H NMR (200MHz, CDCl_3) δ : 2.40 (3H, s), 2.66-2.78 (2H, m), 2.92-3.03 (2H, m), 4.05-4.18 (1H, br), 4.30-4.37 (2H, m), 6.88 (1H, ddd, $J=1.4, 2.8, 8.0\text{Hz}$), 7.08 (1H, dd, $J=4.8, 8.0\text{Hz}$), 7.23-7.30 (3H, m), 7.32-7.39 (3H, m), 7.41-7.51 (4H, m), 7.58-7.65 (3H, m), 7.98 (1H, dd, $J=1.4, 4.8\text{Hz}$), 8.09 (1H, d, $J=2.8\text{Hz}$).

Working Example 48 (Production of Compound 48)

In DMF (3ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added 2-amino-1,3-propanediol (106mg). The mixture was stirred at room temperature for 72 hours, and to the mixture was added water (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give N-[4-[(1,3-dihydroxy-2-propyl)aminomethyl]phenyl]-7-(4-methyl-phenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 48) (60mg) as colorless crystals. mp 189-193°C

Elemental Analysis for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$

Calcd: C, 75.99; H, 6.83; N, 6.33.

30 Found: C, 75.64; H, 6.86; N, 6.11.

IR (KBr) cm^{-1} : 3332, 2931, 1649, 1620, 1597, 1520, 1412, 1319, 1255, 1045, 812

^1H NMR (200MHz, $\text{DMSO}-d_6$) δ : 2.35 (3H, s), 2.53-2.65 (2H, m), 2.80-2.93 (2H, m), 3.28-3.45 (5H, m), 3.73 (2H, s), 4.43 (2H, s), 7.20-7.35 (5H, m), 7.43-7.59 (5H, m), 7.67 (2H, d, $J=8.4\text{Hz}$), 9.90 (1H, s).

Working Example 49 (Production of Compound 49)

In THF (10ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (300mg), and to the mixture was added 4-hydroxypiperidine (235mg). The mixture was refluxed for 24 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give N-[4-(4-hydroxypiperidinomethyl)phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (Compound 49) (271mg) as colorless crystals.
mp 223-224°C

Elemental Analysis for $C_{30}H_{32}N_2O_2$

Calcd: C, 79.61; H, 7.13; N, 6.19.

Found: C, 79.54; H, 7.00; N, 6.15.

IR (KBr) cm^{-1} : 3321, 2937, 1651, 1622, 1597, 1520, 1412, 1319, 1070, 812

^1H NMR (200MHz, DMSO- d_6) δ : 1.28-1.47 (2H, m), 1.63-1.78 (2H, m), 1.88-2.08 (2H, m), 2.25-2.70 (7H, m), 2.80-2.92 (2H, m), 3.23-3.50 (2H, m), 4.50-4.58 (1H, m), 7.17-7.33 (5H, m), 7.45 (1H, s), 7.48-7.60 (4H, m), 7.67 (2H, d, $J=8.0\text{Hz}$), 9.92 (1H, s).

Working Example 50 (Production of Compound 50)

In THF (10ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydro-naphthalene-2-carboxamide (300mg), and to the mixture was added thiomorpholine (233 μ l). The mixture was refluxed for 20 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and

concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-[4-(thiomorpholinomethyl)phenyl]-3,4-dihydro-naphthalene-2-carboxamide (Compound 50) (309mg) as colorless crystals.

mp 178-180°C

Elemental Analysis for $C_{23}H_{20}N_2OS$

Calcd: C, 76.61; H, 6.65; N, 6.16.

Found: C, 76.39; H, 6.71; N, 5.94.

IR (KBr) cm^{-1} : 3307, 2910, 2810, 1648, 1599, 1520, 1412, 1315, 1257, 806

1H NMR (200MHz, $CDCl_3$) δ : 2.40 (3H, s), 2.57-2.75 (10H, m), 2.90-3.03 (2H, m), 3.50 (2H, s), 7.22-7.62 (13H, m).

Working Example 51 (Production of Compound 51)

In THF (10ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (300mg), and to the mixture was added diethanolamine (222 μ l). The mixture was refluxed for 34 hours. The reaction mixture was cooled to room temperature, and to the mixture was added 5% sodium hydrogen carbonate solution (50ml). The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/triethylamine=10/1) and recrystallized from ethyl acetate-hexane to give N-[4-[N,N-bis(2-hydroxyethyl)-aminomethyl]phenyl]-7-(4-methylphenyl)-3,4-dihydro-naphthalene-2-carboxamide (Compound 51) (148mg) as colorless crystals.

mp 150-151°C

Elemental Analysis for $C_{27}H_{32}N_2O_3$

Calcd: C, 76.29; H, 7.06; N, 6.14.

Found: C, 75.90; H, 7.10; N, 6.18.

IR (KBr) cm^{-1} : 3307, 2943, 1645, 1599, 1524, 1412, 1321, 1255, 1036, 804

¹H NMR (200MHz, CDCl₃) δ: 2.40 (3H, s), 2.64-2.75 (6H, m), 2.90-3.00 (2H, m), 3.58-3.70 (6H, m), 7.20-7.37 (6H, m), 7.40-7.51 (4H, m), 7.58 (2H, d, J=8.4Hz), 7.67-7.77 (1H, m).

5 Working Example 52 (Production of Compound 52)

In DMF (5ml) was dissolved N-[4-(chloromethyl)-phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (150mg), and to the mixture was added pyridine (94μl). The mixture was stirred at 70°C for 24 hours, and
10 to the mixture was added water (50ml). The mixture was washed with ethyl acetate. The aqueous layer was allowed to stand at room temperature for 3 hours. The resulting precipitate was filtered and purified with ethyl acetate-methanol to give 1-[7-(4-methylphenyl)-3,4-
15 dihydronaphthalene-2-carboxamido)benzyl]pyridinium chloride (Compound 52) (74mg) as colorless amorphous. Elemental Analysis for C₂₀H₁₇N₂OCl · 0.5H₂O
Calcd: C, 75.70; H, 5.93; N, 5.88.
Found: C, 75.83; H, 6.02; N, 5.63.

20 IR (KBr) cm⁻¹: 3413, 1655, 1595, 1518, 1414, 1317, 1248, 810
¹H NMR (200MHz, DMSO-d₆) δ: 2.35 (3H, s), 2.55-2.67 (2H, m), 2.80-2.93 (2H, m), 5.85 (2H, s), 7.24-7.34 (3H, m), 7.50-7.60 (7H, m), 7.85 (2H, d, J=8.6Hz), 8.14-8.25 (2H, m), 8.64 (1H, t, J=7.7Hz), 9.20-9.30 (2H, m), 10.18 (1H, s).

25 Working Example 53 (Production of Compound 53)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.2g) and sodium cyclohexylsulfide (0.08g) in dimethylformamide (10ml) was stirred at room temperature for 2.5 hours. The
30 solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give
35 crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(cyclohexylthiomethyl)-

phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 53) (0.19g) as colorless crystals. mp 161-162°C.

¹H-NMR (δ ppm, CDCl₃): 1.23-1.42 (6H, m), 1.63-1.75 (2H, m),
5 1.92-2.05 (2H, m), 2.39 (3H, s), 2.49-2.59 (1H, m), 3.07 (2H, t, J=4.5Hz), 3.73 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.2Hz), 7.22-7.34 (5H, m), 7.44-7.59 (7H, m).
IR(KBr) ν : 2928, 2851, 1651cm⁻¹.

Anal. for C₃₁H₃₃NO₂S:

10 Calcd. C, 76.98; H, 6.88; N, 2.90.

Found C, 76.65; H, 6.59; N, 3.09.

Working Example 54 (Production of Compound 54)

In DMF (3ml) was dissolved 3,4-dihydro-N-[4-(4-hydroxypiperidinomethyl)phenyl]-7-(4-methylphenyl)-
15 naphthalene-2-carboxamide (130mg), and to the mixture was added methyl iodide (54 μ l). The mixture was stirred at room temperature for 17 hours, and to the mixture was added ethyl acetate (100ml). The resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give
20 4-hydroxy-1-methyl-1-[4-[7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamido]benzyl]-piperidinium iodide (Compound 54) (138mg, ratio of isomers=58:42) as colorless crystals.

mp 157-161°C

25 Elemental Analysis for C₃₁H₃₃N₂O₂I · 0.5H₂O

Calcd: C, 61.69; H, 6.01; N, 4.64.

Found: C, 61.75; H, 5.84; N, 4.64.

IR (KBr) cm⁻¹: 3396, 1655, 1595, 1520, 1416, 1319, 1250, 812

¹H NMR (200MHz, DMSO-d₆) δ : 1.65-1.90 (2H, m), 1.96-2.20 (2H,
30 m), 2.35 (3H, s), 2.55-2.68 (2H, m), 2.82-3.00 (5H, m), 3.10-3.57 (4H, m), 3.70-3.90 (1H, m), 4.50-4.60 (2H, m), 5.05 (0.42H, d, J=2.8Hz), 5.12 (0.58H, d, J=3.6Hz), 7.22-7.35 (3H, m), 7.42-7.60 (7H, m), 7.83-7.93 (2H, m), 10.18 (1H, s).

35 Working Example 55 (Production of Compound 55)

In DMF (3ml) was dissolved 7-(4-methylphenyl)-N-

[4-(thiomorpholinomethyl)phenyl]-3,4-dihydro-naphthalene-2-carboxamide (160mg), and to the mixture was added methyl iodide (66 μ l). The mixture was stirred at room temperature for 17 hours, and to the mixture was added ethyl acetate (100ml). The resulting precipitate was filtered and recrystallized from ethyl acetate-methanol to give 4-methyl-4-[4-[7-(4-methyl-phenyl)-3,4-dihydro-naphthalene-2-carboxamido]benzyl]-thiomorpholinium iodide (Compound 55) (165mg) as colorless crystals.

mp 183-185°C

Elemental Analysis for $C_{30}H_{33}N_2OSI \cdot 0.2H_2O$

Calcd: C, 60.04; H, 5.61; N, 4.67.

Found: C, 59.91; H, 5.52; N, 4.66.

IR (KBr) cm^{-1} : 3423, 1651, 1597, 1520, 1416, 1319, 1250, 812

1H NMR (200MHz, DMSO- d_6) δ : 2.35 (3H, s), 2.55-2.68 (2H, m), 2.83-3.30 (9H, m), 3.40-3.65 (4H, m), 4.62 (2H, s), 7.25-7.35 (3H, m), 7.45-7.61 (7H, m), 7.90 (2H, d, $J=8.6Hz$), 10.19 (1H, s).

Working Example 56 (Production of Compound 56)

In DMF (3ml) was dissolved N-[4-[N,N-bis(2-hydroxyethyl)aminomethyl]phenyl]-7-(4-methylphenyl)-3,4-dihydronaphthalene-2-carboxamide (100mg), and to the mixture was added methyl iodide (41 μ l). The mixture was stirred at room temperature for 22 hours. The solvent was evaporated and the residue was purified with ethyl acetate-methanol to give bis(2-hydroxyethyl)methyl[4-[7-(4-methylphenyl)-3,4-naphthalene-2-carboxamido]-benzyl]ammonium iodide (Compound 56) (101mg) as colorless amorphous.

Elemental Analysis for $C_{30}H_{33}N_2O_3I \cdot 0.5H_2O$

Calcd: C, 59.31; H, 5.97; N, 4.61.

Found: C, 59.19; H, 5.74; N, 4.68.

IR (KBr) cm^{-1} : 3365, 1651, 1593, 1520, 1416, 1319, 1250, 810

1H NMR (200MHz, DMSO- d_6) δ : 2.35 (3H, s), 2.55-2.67 (2H, m), 2.84-3.01 (5H, m), 3.27-3.55 (4H, m), 3.88-3.98 (4H, m), 4.62 (2H, s), 5.33 (2H, t, $J=4.8Hz$), 7.25-7.35 (3H, m),

7.47-7.60 (7H, m), 7.88 (2H, d, J=8.4Hz), 10.18 (1H, s).
Working Example 57 (Production of Compound 57)

In DMF (3ml) was dissolved (E)-N-[4-(chloromethyl)-phenyl]-3-(4-methylphenyl)cinnamamide (200mg), and to the
5 solution were added 1-(3,4-methylenedioxybenzyl)-
piperazine (158mg) and potassium carbonate (382mg). The
mixture was stirred at room temperature for 16 hours, and
to the mixture was added water (50ml). The mixture was
extracted with ethyl acetate. The organic layer was washed
10 with saturated sodium chloride solution, dried with
anhydrous sodium sulfate, and concentrated under reduced
pressure. The residue was recrystallized from ethyl
acetate-diisopropylether to give (E)-N-[4-[1-(3,4-
methylenedioxybenzyl)-4-piperazinylmethyl]phenyl]-3-(4-
15 methylphenyl)cinnamamide (Compound 57) (266mg) as
colorless crystals.

mp 204-207°C

Elemental Analysis for $C_{23}H_{23}N_3O_2 \cdot 0.5H_2O$

Calcd: C, 75.79; H, 6.54; N, 7.58.

20 Found: C, 76.19; H, 6.48; N, 7.83.

IR (KBr) cm^{-1} : 2939, 2806, 1664, 1626, 1524, 1491, 1246, 1041,
1007, 970, 824, 795

1H NMR (200MHz, $CDCl_3$) δ : 2.30-2.60 (8H, m), 2.41 (3H, s),
3.41 (2H, s), 3.48 (2H, s), 5.93 (2H, s), 6.61 (1H, d,
25 J=15.6Hz), 6.73 (2H, s), 6.84 (1H, s), 7.23-7.32 (4H, m),
7.35-7.60 (8H, m), 7.72 (1H, s), 7.81 (1H, d, J=15.6Hz).

Working Example 58 (Production of Compound 58)

In THF (10ml) was dissolved 7-phenylnaphthalene-2-
carboxylic acid (350mg), and to the solution were added
30 oxalyl chloride (184 μ l) and a drop of DMF. The mixture was
stirred at room temperature for 1 hour and concentrated under
reduced pressure. The residue was dissolved in THF (10ml),
and to the solution were added 1-(4-aminobenzyl)-
piperidine (295mg) and triethylamine (237 μ l) at room
35 temperature. The reaction mixture was stirred at room
temperature for 2 hours, and to the mixture was added water

Found C, 75.14; H, 5.55; N, 2.99.

Working Example 109 (Production of Compound 109)

To a solution of N-(4-(benzylthiomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.12g) in dichloromethane (25ml) was added 70% m-chloroperbenzoic acid (0.06g) at the temperature ranging from -20 to -10°C, and the mixture was stirred for 10 minutes. To the mixture was added sodium thiosulfate solution, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(benzylsulfinylmethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 109) (0.08g) as colorless crystals. mp 208-209°C.

¹H-NMR (δ ppm, CDCl₃): 2.39 (3H, s), 3.07 (2H, t, J=4.5Hz), 3.76-3.94 (4H, m), 4.35 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.2Hz), 7.23-7.27 (6H, m), 7.35-7.53 (7H, m), 7.61 (2H, d, J=8.4Hz), 7.93 (1H, s).

IR (KBr) ν: 3030, 1662 cm⁻¹.

Anal. for C₂₂H₂₁NO₃S·0.2H₂O:

Calcd. C, 75.18; H, 5.80; N, 2.74.

Found C, 75.35; H, 5.81; N, 2.87.

Working Example 110 (Production of Compound 110)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in dichloromethane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was added dropwise to a solution of 4-aminobenzyl 4-methylphenyl sulfone (0.11g) and triethylamine (0.15ml) in tetrahydrofuran (10ml), under

ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((4-methylphenyl)sulfonyl)-methylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 110) (0.13g) as colorless crystals.
mp 230-231°C.

¹H-NMR (δ ppm, CDCl₃): 2.40 (3H, s), 2.43 (3H, s), 3.07 (2H, t, J=4.5Hz), 4.27 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.04-7.10 (3H, m), 7.23-7.26 (5H, m), 7.43-7.55 (8H, m), 7.63 (1H, s).

IR(KBr) ν: 3027, 2884, 1663cm⁻¹.

Anal. for C₂₂H₂₃NO₄S·0.2H₂O:

Calcd. C, 72.90; H, 5.62; N, 2.66.

Found C, 72.74; H, 5.73; N, 2.76.

Working Example 111 (Production of Compound 111)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and N-methylcyclopentylamine (0.07g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethanol-hexane to give N-(4-((N-cyclopentyl-N-methyl)amino-methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 111) (0.1g) as colorless crystals.
mp 171-172°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.45-1.75 (6H, m), 1.80-1.95 (2H, m), 2.13 (3H, s), 2.39 (3H, s), 2.70-2.80 (1H, m), 3.08 (2H, t, $J=4.6\text{Hz}$), 3.50 (2H, s), 4.35 (2H, t, $J=4.6\text{Hz}$), 7.06 (1H, d, $J=8.0\text{Hz}$), 7.22-7.33 (4H, m), 7.43-7.58 (7H, m).

5 IR(KBr) ν : 3340, 2958, 1646cm^{-1} .

Anal. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

Calcd. C, 79.18; H, 7.37; N, 5.96.

Found C, 79.15; H, 7.18; N, 5.96.

Working Example 112 (Production of Compound 112)

10 To a solution of N-(4-hydroxymethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g), triethylamine (0.14ml) and 4-dimethylamino-pyridine (catalytic amount) in dichloromethane was dropwise added methanesulfonyl chloride (0.04ml) under ice-cooling, 15 and the mixture was stirred for 15 minutes. To the mixture was added N-methylcyclohexylamine (0.15ml), and the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 20 crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-cyclohexyl-N-methyl)-aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 112) (0.03g) as colorless crystals.

25 mp $176-177^\circ\text{C}$.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.15-1.35 (6H, m), 1.70-1.95 (4H, m), 2.23 (3H, s), 2.39 (3H, s), 2.39-2.55 (1H, m), 3.08 (2H, t, $J=4.6\text{Hz}$), 3.59 (2H, s), 4.37 (2H, t, $J=4.6\text{Hz}$), 7.06 (1H, d, $J=8.0\text{Hz}$), 7.23-7.35 (5H, m), 7.44-7.58 (7H, m).

30 IR(KBr) ν : 2930, 2853, 1651cm^{-1} .

Anal. for $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_2 \cdot 0.4\text{H}_2\text{O}$:

Calcd. C, 78.78; H, 7.60; N, 5.74.

Found C, 78.97; H, 7.49; N, 5.94.

Working Example 113 (Production of Compound 113)

35 A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.09g),

N-methylcycloheptylamine (0.04g) and potassium carbonate (0.1g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-cycloheptyl-
5 N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 113) (0.08g) as colorless crystals.
mp 167-168°C.

¹H-NMR (δ ppm, CDCl₃): 1.35-1.55 (8H, m), 1.55-1.80 (2H, m),
15 1.80-1.95 (2H, m), 2.16 (3H, s), 2.39 (3H, s), 2.55-2.70 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.49 (2H, s), 4.35 (2H, t, J=4.6Hz), 7.05 (1H, d, J=8.4Hz), 7.22-7.33 (4H, m), 7.43-7.58 (7H, m).

IR(KBr) ν: 2927, 1650cm⁻¹.

20 Anal. for C₃₃H₃₈N₂O₂·0.1H₂O:
Calcd. C, 79.83; H, 7.76; N, 5.64.
Found C, 79.62; H, 7.43; N, 5.53.

Working Example 114 (Production of Compound 114)

A solution of N-(4-chloromethylphenyl)-7-(4-methyl-
25 phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g) and cyclohexylamine (0.17ml) in dimethylformamide (10ml) was stirred at room temperature for 2.5 hours. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give
30 crude crystals, which were recrystallized from ethanol-hexane to give N-(4-((cyclohexylamino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 114) (0.09g) as colorless crystals.
mp 183-184°C.

35 ¹H-NMR(δ ppm, CDCl₃): 1.17-1.30 (6H, m), 1.58-1.82 (4H, m), 2.39 (3H, s), 2.45-2.60 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.81

(2H, s), 4.35 (2H, t, J=4.6Hz), 7.05 (1H, d, J=8.4Hz),
7.22-7.34 (5H, m), 7.43-7.55 (6H, m), 7.72 (1H, s).
IR(KBr) ν : 2928, 2853, 1647 cm^{-1} .

Anal. for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$:

5 Calcd. C, 78.28; H, 7.42; N, 5.89.

Found C, 78.56; H, 7.12; N, 6.01.

Working Example 115 (Production of Compound 115)

A solution of N-(4-chloromethylphenyl)-7-(4-methyl-
phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15g)
10 and aniline (0.1ml) in dimethylformamide (10ml) was stirred
at room temperature over night. The solvent was evaporated,
and to the residue was added water. The mixture was
extracted with ethyl acetate. The organic layer was washed
with water and saturated sodium chloride solution, and dried
15 with anhydrous magnesium sulfate. Under reduced pressure,
the solvent was evaporated, and the residue was purified
with silica gel column (ethyl acetate/hexane) to give crude
crystals, which were recrystallized from ethanol-hexane to
give N-(4-((phenylamino)methyl)-phenyl)-7-(4-methyl-
20 phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 115) (0.1g) as colorless crystals.
mp 157-158°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 2.39 (3H, s), 3.07 (2H, t, J=4.8Hz),
4.31 (2H, s), 4.35 (2H, t, J=4.8Hz), 6.62-6.76 (3H, m), 7.06
25 (1H, d, J=8.4Hz), 7.18-7.22 (5H, m), 7.36 (2H, d, J=8.4Hz),
7.43-7.60 (6H, m).

IR(KBr) ν : 1652, 1602 cm^{-1} .

Anal. for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2$:

Calcd. C, 80.84; H, 6.13; N, 6.08.

30 Found C, 80.57; H, 6.09; N, 6.06.

Working Example 116 (Production of Compound 116)

A suspension of N-(4-chloromethylphenyl)-7-(4-
methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(0.15g), N-methylaniline (0.06ml) and potassium carbonate
35 (0.15g) in dimethylformamide (10ml) was stirred at room
temperature over night. The solvent was evaporated, and to

- the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was
- 5 evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-methyl-N-phenyl)aminomethyl)phenyl)-7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 116) (0.15g) as colorless crystals.
- 10 mp 164-165°C.
- ¹H-NMR (δ ppm, CDCl₃): 2.39 (3H, s), 3.00 (3H, s), 3.06 (2H, t, J=4.6Hz), 4.34 (2H, t, J=4.6Hz), 4.51 (2H, s), 6.68-6.77 (3H, m), 7.05 (1H, d, J=8.4Hz), 7.19-7.26 (6H, m), 7.43-7.54 (6H, m), 7.60 (1H, s).
- 15 IR(KBr) ν: 3344, 3020, 1644cm⁻¹.
- Anal. for C₂₂H₂₀N₂O₂:
Calcd. C, 80.98; H, 6.37; N, 5.90.
Found C, 80.64; H, 6.32; N, 5.85.
- Working Example 117 (Production of Compound 117)
- 20 A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g), benzylamine hydrochloride (0.5g) and potassium carbonate (0.6g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated,
- 25 and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified
- 30 with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((benzylamino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 117)
- 35 (0.08g) as colorless crystals.
mp 147-148°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 2.39 (3H, s), 3.08 (2H, t, $J=4.6\text{Hz}$), 3.80 (2H, s), 3.81 (2H, s), 4.35 (2H, t, $J=4.6\text{Hz}$), 7.06 (1H, d, $J=8.4\text{Hz}$), 7.22-7.36 (9H, m), 7.43-7.61 (7H, m).
 IR(KBr) $\tilde{\nu}$: 3028, 1652 cm^{-1} .

5 Anal. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2 \cdot 0.1\text{H}_2\text{O}$:

Calcd. C, 80.68; H, 6.39; N, 5.88.

Found C, 80.43; H, 6.23; N, 5.95.

Working Example 118 (Production of Compound 118)

10 A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g), N-methylbenzylamine (0.05ml) and potassium carbonate (0.1g) in dimethylformamide (5ml) was stirred at room temperature for 2 hours. The solvent was evaporated, and to the residue was added water. The mixture was
15 extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which
20 were recrystallized from ethyl acetate-hexane to give N-(4-((N-benzyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 118) (0.09g) as colorless crystals.
mp 157-158 $^{\circ}\text{C}$.

25 $^1\text{H-NMR}$ (δ ppm, CDCl_3): 2.18 (3H, s), 2.39 (3H, s), 3.06 (2H, t, $J=4.6\text{Hz}$), 3.50 (2H, s), 3.52 (2H, s), 4.34 (2H, t, $J=4.6\text{Hz}$), 7.05 (1H, d, $J=8.0\text{Hz}$), 7.22-7.30 (3H, m), 7.33-7.37 (5H, m), 7.43-7.57 (7H, m), 7.63 (1H, s).

IR(KBr) ν : 3336, 1643 cm^{-1} .

Anal. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

30 Calcd. C, 80.52; H, 6.63; N, 5.69.

Found C, 80.61; H, 6.49; N, 5.54.

Working Example 119 (Production of Compound 119)

35 A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and diisopropylamine (0.1ml) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was

evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((diisopropylamino)methyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 119) (0.11g) as colorless crystals.

mp 152-153°C.

¹H-NMR(δ ppm, CDCl₃): 1.02 (12H, d, J=6.6Hz), 2.39 (3H, s), 2.98-3.10 (4H, m), 3.62 (2H, s), 4.35 (2H, t, J=4.8Hz), 7.05 (1H, d, J=8.6Hz), 7.24 (2H, d, J=8.0Hz), 7.35-7.55 (9H, m). IR(KBr) ν: 2964, 1646cm⁻¹.

Anal. for C₂₁H₂₆N₂O₂:
Calcd. C, 79.45; H, 7.74; N, 5.98.
Found C, 79.18; H, 7.66; N, 5.93.

Working Example 120 (Production of Compound 120)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and N-ethylcyclohexylamine (0.11ml) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-cyclohexyl-N-ethyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 120) (0.1g) as colorless crystals.

mp 166-167°C.

¹H-NMR(δ ppm, CDCl₃): 0.98 (3H, t, J=7.2Hz), 1.02-1.26 (6H, m), 1.60-1.80 (4H, m), 2.39 (3H, s), 2.48-2.59 (3H, m), 3.08 (2H, t, J=4.5Hz), 3.59 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.05

(1H, d, J=8.4Hz), 7.24 (2H, d, J=7.6Hz), 7.35 (2H, d, J=8.4Hz), 7.43-7.56 (7H, m).

IR(KBr) ν : 2929, 1648 cm^{-1} .

Anal. for $\text{C}_{33}\text{H}_{36}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

5 Calcd. C, 79.55; H, 7.77; N, 5.62.

Found C, 79.65; H, 7.63; N, 5.66.

Working Example 121 (Production of Compound 121)

A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
10 (0.1g), 4-ethyl-amino-1-benzylpiperidine (0.11g) and potassium carbonate (0.05g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was
15 washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from diethyl ether-hexane to give
20 N-(4-((N-(1-benzylpiperidin-4-yl)-N-ethyl)amino-methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 121) (0.13g) as colorless crystals.

mp 121-122°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.98 (3H, t, J=7.1Hz), 1.55-1.75 (4H, m), 1.87-2.00 (2H, m), 2.39 (3H, s), 2.49-2.60 (3H, m), 2.90-2.96 (2H, m), 3.08 (2H, t, J=4.4Hz), 3.48 (2H, s), 3.60 (2H, s), 4.36 (2H, t, J=4.4Hz), 7.06 (1H, d, J=8.2Hz), 7.23-7.35 (9H, m), 7.44-7.55 (7H, m).

IR(KBr) ν : 2939, 1652 cm^{-1} .

30 Anal. for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_2$:

Calcd. C, 79.97; H, 7.40; N, 7.17.

Found C, 79.95; H, 7.50; N, 7.28.

Working Example 122 (Production of Compound 122)

A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
35 (0.1g), amino-methylcyclohexane (0.05g) and potassium

- carbonate (0.1g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((cyclohexylmethyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 122) (0.06g) as colorless crystals. mp 154-155°C.
- ¹H-NMR (δ ppm, CDCl₃): 0.88-0.99 (2H, m), 1.17-1.26 (4H, m), 1.43-1.56 (1H, m), 1.65-1.78 (4H, m), 2.39 (3H, s), 2.45 (2H, d, J=6.6Hz), 3.07 (2H, t, J=4.5Hz), 3.76 (2H, s), 4.35 (2H, t, J=4.5Hz), 7.05 (1H, d, J=8.4Hz), 7.22-7.33 (5H, m), 7.43-7.61 (6H, m).
- IR(KBr) ν: 3357, 2918, 1648cm⁻¹.
Anal. for C₂₂H₂₆N₂O₂·0.2H₂O:
Calcd. C, 79.37; H, 7.58; N, 5.78.
Found C, 79.58; H, 7.50; N, 5.80.
- Working Example 123 (Production of Compound 123)
- A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and 1-methyl-4-methylaminopiperidine (0.1ml) in dimethylformamide (5ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-methyl-N-(1-methylpiperidin-4-yl))aminomethyl)phenyl)-7-(4-

methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 123) (0.03g) as colorless crystals.

mp 183-184°C.

¹H-NMR(δ ppm, CDCl₃): 1.67-2.05 (6H, m), 2.20 (3H, s), 2.28
5 (3H, s), 2.39 (3H, s), 2.38-2.45 (1H, m), 2.91-2.96 (1H,
m), 3.08 (2H, t, J=4.6Hz), 3.56 (2H, s), 4.36 (2H, t, J=4.5Hz),
7.06 (1H, d, J=8.0Hz), 7.22-7.33 (4H, m), 7.44-7.59 (7H,
m).

IR(KBr) ν: 2939, 2785, 1652cm⁻¹.

10 Anal. for C₂₂H₂₇N₃O₂:

Calcd. C, 77.54; H, 7.52; N, 8.48.

Found C, 77.34; H, 7.57; N, 8.56.

Working Example 124 (Production of Compound 124)

To a solution of 7-(4-(4-methylpiperazin-1-yl)-
15 phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid
(0.12g), 4-(N-methyl-N-(tetrahydropyran-4-yl)amino-
methyl)aniline (0.08g) and 1-hydroxybenzotriazole(0.05g)
in dimethylformamide (15ml) was added 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydro-chloride (0.1g),
20 under ice-cooling. Under nitrogen atmosphere, the mixture
was cooled to room temperature. To the mixture were added
4-dimethylaminopyridine (catalytic amount) and triethyl-
amine (0.14ml), and the mixture was stirred over night. The
solvent was evaporated, and to the residue was added water.
25 The mixture was extracted with ethyl acetate. The organic
layer was washed with water and saturated sodium chloride
solution, and dried with anhydrous magnesium sulfate.
Under reduced pressure, the solvent was evaporated, and the
residue was purified with silica gel column (ethyl acetate/
30 methanol/triethylamine) to give crude crystals, which were
recrystallized from ethyl acetate-hexane to give 7-(4-
(4-methylpiperazin-1-yl)phenyl)-N-(4-((N-tetrahydro-
pyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-
benzoxepine-4-carboxamide (Compound 124) (0.15g) as
35 colorless crystals.
mp 220-221°C.

¹H-NMR (δ ppm, CDCl₃): 1.64-1.75 (4H, m), 2.22 (3H, s), 2.37 (3H, s), 2.58-2.71 (5H, m), 3.08 (2H, t, J=4.6Hz), 3.25-3.32 (4H, m), 3.37 (2H, dt, J=2.8, 11.4Hz), 3.58 (2H, s), 4.01-4.07 (2H, m), 4.35 (2H, t, J=4.6Hz), 6.97-7.06 (3H, m), 7.32 (2H, d, J=8.4Hz), 7.41-7.58 (7H, m).

IR(KBr) ν: 2946, 2841, 1663cm⁻¹.

Anal. for C₃₅H₄₂N₂O₃ · 0.5H₂O:

Calcd. C, 73.01; H, 7.53; N, 9.73.

Found C, 73.25; H, 7.46; N, 9.72.

10 Working Example 125 (Production of Compound 125)

A solution of N-(4-((N-(1-t-butoxycarbonyl-piperidin-4-yl)-N-methylamino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.14g) and trifluoro-acetic acid (5ml) in dichloromethane (20ml) was stirred at room temperature for 1.5 hours. The reaction mixture was neutralized with sodium hydrogen carbonate solution, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethanol-hexane to give N-(4-((N-methyl-N-(piperidin-4-yl))aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 125) (0.08g) as colorless crystals. mp 129-130°C.

¹H-NMR (δ ppm, CDCl₃): 1.68-1.95 (4H, m), 2.22 (3H, s), 2.39 (3H, s), 2.61-2.79 (3H, m), 3.08 (2H, t, J=4.5Hz), 3.25-3.33 (2H, m), 3.58 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.4Hz), 7.23-7.33 (4H, m), 7.44-7.60 (7H, m). IR(KBr) ν: 2929, 1683cm⁻¹.

Working Example 126 (Production of Compound 126) and Working Example 127 (Production of Compound 127)

35 A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide

(0.1g), N,4-dimethylcyclohexylamine hydrochloride (0.08g) and potassium carbonate (0.17g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture
5 was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give each
10 of crude crystals, which was recrystallized from ethyl acetate-hexane to give each isomer of N-(4-((N-methyl-N-(4-methylcyclohexyl)amino-methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 126 (0.05g), Compound 127(0.03g)) as colorless
15 crystals.

(Compound 126):

mp 144-145°C.

¹H-NMR(δ ppm, CDCl₃): 0.96 (3H, d, J=6.8Hz), 1.40-1.80 (9H, m), 2.17 (3H, s), 2.20-2.40 (1H, m), 2.39 (3H, s), 3.08 (2H, t, J=4.5Hz), 3.55 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.05 (1H, d, J=8.4Hz), 7.22-7.34 (4H, m), 7.43-7.58 (7H, m).

IR(KBr) ν: 2927, 1650cm⁻¹.

Anal. for C₃₃H₃₈N₂O₂·0.2H₂O:

Calcd. C, 79.55; H, 7.77; N, 5.62.

25 Found C, 79.59; H, 7.68; N, 5.84.

(Compound 127):

mp 183-184°C.

¹H-NMR(δ ppm, CDCl₃): 0.87 (3H, d, J=6.6Hz), 0.89-1.02 (2H, m), 1.26-1.89 (7H, m), 2.20 (3H, s), 2.20-2.40 (1H, m), 2.39 (3H, s), 3.08 (2H, t, J=4.6Hz), 3.56 (2H, s), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.34 (5H, m),

7.44-7.55 (6H, m).

IR(KBr) ν: 2925, 1654cm⁻¹.

Anal. for C₃₃H₃₈N₂O₂·0.2H₂O:

35 Calcd. C, 79.55; H, 7.77; N, 5.62.

Found C, 79.48; H, 7.70; N, 5.83.

Working Example 128 (Production of Compound 128)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (7ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.12g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(N-methyl-(N-tetrahydropyran-4-yl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 128) (0.19g) as colorless crystals. mp 162-163°C.

¹H-NMR(δ ppm, CDCl₃): 1.59-1.74 (4H, m), 2.20 (3H, s), 2.39 (3H, s), 2.58-2.66 (1H, m), 3.07 (2H, t, J=4.5Hz), 3.37 (2H, dt, J=2.8, 11.0Hz), 3.56 (2H, s), 4.01-4.06 (2H, m), 4.35 (2H, t, J=4.5Hz), 7.05 (1H, d, J=8.4Hz), 7.22-7.33 (4H, m), 7.43-7.56 (6H, m), 7.62 (1H, s).

IR(KBr) ν: 3296, 2950, 1654cm⁻¹.

Anal. for C₂₁H₂₄N₂O₃ · 0.2H₂O:

Calcd. C, 76.58; H, 7.13; N, 5.76.

Found C, 76.51; H, 7.07; N, 5.53.

Working Example 129 (Production of Compound 129)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (5ml) were added oxalyl chloride (0.14ml) and

dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-(N-methyl-N-(tetrahydropyran-3-yl)amino-methyl)aniline (0.13g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-tetrahydropyran-3-yl-N-methyl)aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 129) (0.18g) as colorless crystals. mp 158-159°C.

¹H-NMR (δ ppm, CDCl₃): 1.57-1.75 (3H, m), 2.00-2.05 (1H, m), 2.21 (3H, s), 2.39 (3H, s), 2.55-2.68 (1H, m), 3.08 (2H, t, J=4.7Hz), 3.22-3.39 (2H, m), 3.59 (2H, s), 3.84-3.90 (1H, m), 4.04-4.07 (1H, m), 4.37 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.0Hz), 7.23-7.32 (4H, m), 7.44-7.55 (7H, m).
IR(KBr) ν: 2941, 1652cm⁻¹.

Anal. for C₂₁H₂₃N₂O₃:

Calcd. C, 77.15; H, 7.10; N, 5.80.

Found C, 77.12; H, 7.02; N, 5.88.

30 Working Example 130 (Production of Compound 130)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (7ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount), under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved

in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-indan-2-yl-N-methyl)aminomethyl)-aniline (0.14g) and triethyl-amine (0.23ml) in tetrahydrofuran (15ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-ethanol-hexane to give N-(4-((N-indan-2-yl-N-methyl)amino-methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 130) (0.23g) as colorless crystals.

mp 204-205°C.

¹H-NMR(δ ppm, CDCl₃): 2.19 (3H, s), 2.39 (3H, s), 2.94-3.18 (6H, m), 3.41-3.48 (1H, m), 3.57 (2H, s), 4.36 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.4Hz), 7.16-7.22 (6H, m), 7.33-7.57 (9H, m).

IR(KBr) ν: 1654cm⁻¹.

Anal. for C₂₃H₂₄N₂O₂ · 0.2H₂O:

Calcd. C, 81.11; H, 6.69; N, 5.41.

Found C, 81.06; H, 6.57; N, 5.49.

25 Working Example 131 (Production of Compound 131)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (6ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of (E)-4-((N-4-t-butylcyclohexyl-N-methyl)aminomethyl)aniline (0.15g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over

night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate.

The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give (E)-N-(4-((N-(4-t-butylcyclohexyl)-N-methyl)aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 131) (0.22g) as colorless crystals.
mp 225-226°C.

¹H-NMR(δ ppm, CDCl₃): 0.84 (9H, s), 0.95-1.05 (2H, m), 1.22-1.33 (2H, m), 1.82-1.95 (5H, m), 2.20 (3H, s), 2.30-2.45 (1H, m), 2.39 (3H, s), 3.08 (2H, t, J=4.6Hz), 3.55 (2H, s), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.0Hz), 7.22-7.34 (4H, m), 7.44-7.55 (7H, m).

IR(KBr) ν: 2943, 1652cm⁻¹.

Anal. for C₂₆H₃₄N₂O₂:

Calcd. C, 80.56; H, 8.26; N, 5.22.

Found C, 80.30; H, 8.42; N, 5.32.

Working Example 132 (Production of Compound 132)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (6ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount), under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of (Z)-4-((N-4-t-butylcyclohexyl-N-methyl)-aminomethyl)aniline (0.15g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium

sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from diethyl ether-hexane to give (Z)-N-(4-((N-(4-t-butylcyclohexyl)-N-methyl)aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 132) (0.2g) as colorless crystals.

mp 169-170°C.

¹H-NMR (δ ppm, CDCl₃): 0.89 (9H, s), 1.05-1.20 (1H, m), 1.36-1.50 (6H, m), 2.06 (3H, s), 2.06-2.14 (2H, m), 2.30-2.32 (1H, m), 2.39 (3H, s), 3.09 (2H, t, J=4.8Hz), 3.50 (2H, s), 4.37 (2H, t, J=4.8Hz), 7.06 (1H, d, J=8.4Hz), 7.23-7.35 (4H, m), 7.44-7.54 (7H, m).

IR(KBr) ν: 2941, 1648cm⁻¹.

Anal. for C₂₈H₃₄N₂O₂ · 0.2H₂O:

Calcd. C, 80.02; H, 8.28; N, 5.18.

Found C, 80.23; H, 8.30; N, 5.22.

Working Example 133 (Production of Compound 133)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (6ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)aminomethyl)aniline (0.13g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from diethyl ether-hexane to give N-(4-((N-methyl-N-(3,5-dimethylcyclohexyl))aminomethyl)phenyl)-7-(4-

methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 133) (0.22g) as colorless crystals.
mp 135-136°C.

¹H-NMR(δ ppm, CDCl₃): 0.45-0.68 (1H, m), 0.84 (3H, s), 0.87
5 (3H, s), 0.96-1.03 (2H, m), 1.65-2.05 (5H, m), 2.06 (3H,
s), 2.39 (3H, s), 2.39-2.42 (1H, m), 3.08 (2H, t, J=4.7Hz),
3.50 (2H, s), 4.36 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.4Hz),
7.16-7.32 (4H, m), 7.44-7.54 (7H, m).
IR(KBr) ν: 2947, 1652cm⁻¹.

10 Anal. for C₂₃H₂₆N₂O₂:

Calcd. C, 80.28; H, 7.93; N, 5.51.

Found C, 80.19; H, 7.95; N, 5.54.

Working Example 134 (Production of Compound 134)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-
15 1-benzoxepine-4-carboxylic acid (0.15g) in dichloro-
methane (6ml) were added oxalyl chloride (0.14ml) and
dimethylformamide (catalytic amount) under ice-cooling,
and the mixture was stirred at room temperature for 2 hours.
The solvent was evaporated, and the residue was dissolved
20 in tetrahydrofuran. The mixture was dropwise added to a
solution of 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)-
aminomethyl)aniline (0.13g) and triethylamine (0.23ml) in
tetrahydrofuran (10ml), under ice-cooling. Under
nitrogen atmosphere, the mixture was stirred at room
25 temperature over night. The solvent was evaporated, and to
the residue was added water. The mixture was extracted with
ethyl acetate. The organic layer was washed with water and
saturated sodium chloride solution, and dried with anhydrous
magnesium sulfate. Under reduced pressure, the solvent was
30 evaporated to give crude crystals, which were recrystallized
from ethyl acetate-hexane to give N-(4-((N-methyl-N-
(3,5-dimethylcyclohexyl))aminomethyl)phenyl)-7-(4-
methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 134) (0.2g) as colorless crystals.
35 mp 173-174°C.

¹H-NMR(δ ppm, CDCl₃): 0.43-0.60 (1H, m), 0.81-0.99 (2H, m),

0.91 (3H, s), 0.95 (3H, s), 1.30-1.58 (3H, m), 1.79-1.84 (2H, m), 2.19 (3H, s), 2.39 (3H, s), 2.48-2.60 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.55 (2H, s), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.33 (4H, m), 7.44-7.55 (7H, m).

5 IR(KBr) ν : 2950, 1652 cm^{-1} .

Anal. for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

Calcd. C, 79.71; H, 7.95; N, 5.47.

Found C, 79.83; H, 7.83; N, 5.54.

Working Example 135 (Production of Compound 135)

10 To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.12g) in dichloromethane (5ml) were added oxalyl chloride (0.11ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours.

15 The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)-aminomethyl)aniline (0.1g) and triethylamine (0.17ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate.

20 The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from diethyl ether-hexane to give N-(4-((N-methyl-N-(3,5-dimethylcyclohexyl))aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 135) (0.08g) as pale yellow crystals. mp 99-100°C.

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.82-1.13 (8H, m), 1.40-1.53 (2H, m), 1.64-1.85 (3H, m), 2.08-2.18 (1H, m), 2.18 (3H, s), 2.39 (3H, s), 2.69-2.81 (1H, m), 3.08 (2H, t, J=4.8Hz), 3.54 (2H, s), 4.35 (2H, t, J=4.8Hz), 7.05 (1H, d, J=8.2Hz),

7.22-7.33 (4H, m), 7.43-7.58 (7H, m).

IR(KBr) ν : 2923, 1652 cm^{-1} .

Anal. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$:

Calcd. C, 78.88; H, 7.98; N, 5.41.

5 Found C, 78.88; H, 7.74; N, 5.50.

Working Example 136 (Production of Compound 136)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (5ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-methyl-N-n-propyl)aminomethyl)aniline (0.1g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from diethyl ether-hexane to give N-(4-((N-methyl-N-n-propyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 136) (0.1g) as colorless crystals.

mp 142-143 $^{\circ}\text{C}$.

30 $^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.90 (3H, t, $J=7.3\text{Hz}$), 1.48-1.59 (2H, m), 2.19 (3H, s), 2.29-2.37 (2H, m), 2.39 (3H, s), 3.08 (2H, t, $J=4.4\text{Hz}$), 3.47 (2H, s), 4.36 (2H, t, $J=4.4\text{Hz}$), 7.06 (2H, d, $J=8.4\text{Hz}$), 7.22-7.33 (4H, m), 7.43-7.57 (7H, m).

IR(KBr) ν : 2962, 1652, 1517 cm^{-1} .

35 Anal. for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

Calcd. C, 78.42; H, 7.35; N, 6.31.

Found C,78.41; H,7.21; N,6.26.

Working Example 137 (Production of Compound 137)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and N-methyl-n-butylamine (0.06g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-n-butyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 137) (0.09g) as colorless crystals.

mp 138-139°C.

¹H-NMR(δ ppm, CDCl₃): 0.91 (3H, t, J=7.2Hz), 1.27-1.55 (4H, m), 2.19 (3H, s), 2.33-2.39 (2H, m), 2.39 (3H, s), 3.08 (2H, t, J=4.5Hz), 3.47 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.2Hz), 7.22-7.33 (4H, m), 7.44-7.58 (7H, m).

IR(KBr) ν: 2956, 2931, 1652cm⁻¹.

Anal. for C₂₆H₂₈N₂O₂·0.2H₂O:

Calcd. C,78.64; H,7.57; N,6.11.

Found C,78.83; H,7.44; N,6.19.

Working Example 138 (Production of Compound 138)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (5ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-isopropyl-N-methyl)aminomethyl)aniline (0.1g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture

was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-isopropyl-N-methyl)-aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 138) (0.18g) as colorless crystals.
mp 181-182°C.

¹H-NMR (δ ppm, CDCl₃): 1.07 (6H, d, J=6.6Hz), 2.15 (3H, s), 2.39 (3H, s), 2.83-2.96 (1H, m), 3.08 (2H, t, J=4.7Hz), 3.49 (2H, s), 4.36 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.34 (4H, m), 7.44-7.55 (7H, m).
IR(KBr) ν: 2968, 1652cm⁻¹.

Anal. for C₂₂H₂₂N₂O₂:

Calcd. C, 79.06; H, 7.32; N, 6.36.

Found C, 78.87; H, 7.30; N, 6.33.

20 Working Example 139 (Production of Compound 139)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (5ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-sec-butyl-N-methyl)aminomethyl)aniline (0.12g) and triethylamine (0.23ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the

residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-sec-butyl-N-methyl)-aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 139) (0.12g) as colorless crystals.

mp 152-153°C.

¹H-NMR(δ ppm, CDCl₃): 0.89-1.01 (6H, m), 1.22-1.39 (1H, m), 1.50-1.67 (1H, m), 2.13 (3H, s), 2.39 (3H, s), 2.54-2.65 (1H, m), 3.08 (2H, t, J=4.7Hz), 3.44 (1H, d, J=13.2Hz), 3.56 (1H, d, J=13.2Hz), 4.36 (2H, t, J=4.7Hz), 7.06 (2H, d, J=8.0Hz), 7.22-7.35 (4H, m), 7.44-7.54 (7H, m).

IR(neat) ν: 2964, 1652cm⁻¹.

Anal. for C₃₀H₃₄N₂O₂·0.2H₂O:

Calcd. C, 78.64; H, 7.57; N, 6.11.

Found C, 78.88; H, 7.39; N, 6.16.

Working Example 140 (Production of Compound 140)

A solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) and N-methylisobutylamine (0.06g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water.

The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate.

Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-isobutyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 140) (0.08g) as colorless crystals.

mp 137-138°C.

¹H-NMR(δ ppm, CDCl₃): 0.90 (6H, d, J=6.6Hz), 1.78-1.88 (1H, m), 2.10 (2H, d, J=7.4Hz), 2.16 (3H, s), 2.39 (3H, s), 3.08 (2H, t, J=4.6Hz), 3.44 (2H, s), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.0Hz), 7.23-7.34 (4H, m), 7.44-7.57 (7H, m).

IR(KBr) ν : 2954, 1652 cm^{-1} .

Anal. for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_2$:

Calcd. C, 79.26; H, 7.54; N, 6.16.

Found C, 78.99; H, 7.38; N, 6.21.

5 Working Example 141 (Production of Compound 141)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in dichloromethane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture
10 was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-t-butyl-N-methyl)amino-methyl)aniline (0.08g) and triethylamine (0.12ml) in tetrahydrofuran (10ml), under
15 ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution,
20 and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-t-butyl-N-methyl)amino-methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
25 (Compound 141) (0.12g) as colorless crystals.
mp 122-123 $^{\circ}\text{C}$.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.16 (9H, s), 2.09 (3H, s), 2.39 (3H, s), 3.08 (2H, t, $J=4.7\text{Hz}$), 3.49 (2H, s), 4.36 (2H, t, $J=4.7\text{Hz}$), 7.06 (1H, d, $J=8.4\text{Hz}$), 7.23-7.36 (4H, m), 7.44-7.54 (7H,
30 m).

IR(KBr) ν : 2971, 1651, 1599, 1516 cm^{-1} .

Anal. for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_2$:

Calcd. C, 79.26; H, 7.54; N, 6.16.

Found C, 79.16; H, 7.55; N, 5.98.

35 Working Example 142 (Production of Compound 142)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-

- 1-benzoxepine-4-carboxylic acid (0.1g) in dichloromethane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-((N-methyl-N-(pentan-3-yl))aminomethyl)aniline (0.08g) and triethylamine (0.12ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-methyl-N-(pentan-3-yl))aminomethyl)phenyl)-7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 142) (0.12g) as colorless crystals.
- mp 133-134°C.
- ¹H-NMR(δ ppm, CDCl₃): 0.94 (6H, t, J=7.5Hz), 1.26-1.53 (4H, m), 2.13 (3H, s), 2.24-2.31 (1H, m), 2.40 (3H, s), 3.09 (2H, t, J=4.4Hz), 3.55 (2H, s), 4.37 (2H, t, J=4.4Hz), 7.06 (1H, d, J=8.4Hz), 7.17-7.36 (4H, m), 7.44-7.54 (7H, m).
- IR(KBr) ν: 2930, 1649, 1597, 1518cm⁻¹.
- Anal. for C₃₁H₃₆N₂O₂:
- Calcd. C, 79.45; H, 7.74; N, 5.98.
- Found C, 79.06; H, 7.56; N, 5.98.
- Working Example 143 (Production of Compound 143)
- To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in dichloromethane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetra-

- hydrofuran. The mixture was dropwise added to a solution of 4-((N-methyl-N-(norbornan-2-yl))aminomethyl)aniline (0.09g) and triethylamine (0.12ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate.
- Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane). The purified product was dissolved in ethyl acetate (10ml), and to the mixture was added 4N hydrochloric acid-ethyl acetate solution (0.2ml) under ice-cooling. The solvent was evaporated to give crude crystals, which were recrystallized from ethanol-hexane to give N-(4-((N-methyl-N-(norbornan-2-yl))aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide hydrochloride (Compound 143) (0.16g) as colorless crystals.
- mp 268-269°C (dec.).
- ¹H-NMR (δ ppm, DMSO-d₆): 1.24-1.55 (6H, m), 1.99-2.15 (3H, m), 2.28 (1H, br), 2.34 (3H, s), 2.51-2.63 (3H, m), 2.82 (1H, br), 3.00 (2H, br), 4.04-4.45 (4H, m), 7.06 (1H, d, J=8.4Hz), 7.33 (2H, d, J=7.8Hz), 7.38 (1H, s), 7.48-7.59 (5H, m), 7.75-7.85 (3H, m), 9.52 (0.5H, br), 9.83 (0.5H, br), 10.18 (1H, s).
- IR(KBr) ν: 2957, 2492, 1661 cm⁻¹.
- Anal. for C₃₃H₃₇ClN₂O₂·0.2H₂O:
- Calcd. C, 74.40; H, 7.08; N, 5.26.
- Found C, 74.34; H, 7.05; N, 5.19.
- Working Example 144 (Production of Compound 144)
- To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (5ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours.

The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-(2-(N-cyclohexyl-N-methyl)aminoethyl)-aniline (0.15g) and triethylamine (0.23ml) in tetrahydrofuran (15ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(2-((N-cyclohexyl-N-methyl)amino)ethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 144) (0.23g) as colorless crystals.

mp 154-155°C.

¹H-NMR(δ ppm, CDCl₃): 1.18-1.30 (6H, m), 1.65-1.80 (4H, m), 2.35 (3H, s), 2.39 (3H, s), 2.39-2.50 (1H, m), 2.66-2.73 (4H, m), 3.08 (2H, t, J=4.6Hz), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.4Hz), 7.18-7.26 (4H, m), 7.44-7.55 (7H, m). IR(KBr) ν: 2929, 2854, 1648cm⁻¹.

Anal. for C₃₃H₃₉N₂O₂ · 0.3H₂O:

Calcd. C, 79.26; H, 7.78; N, 5.60.

Found C, 79.26; H, 7.48; N, 5.62.

Working Example 145 (Production of Compound 145)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g) in dichloromethane (5ml) were added oxalyl chloride (0.1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-(1-hydroxy-2-piperidino-ethyl)aniline (0.09g) and triethylamine (0.12ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was

stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(1-hydroxy-2-piperidinoethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 145) (0.14g) as colorless crystals.

mp 212-213°C.

¹H-NMR(δ ppm, CDCl₃): 1.44-1.52 (2H, m), 1.56-1.69 (4H, m), 2.32-2.47 (4H, m), 2.40 (3H, s), 2.65-2.74 (2H, m), 3.08 (2H, t, J=4.5Hz), 4.37 (2H, t, J=4.5Hz), 4.72 (1H, dd, J=3.8, 10.0Hz), 7.06 (1H, d, J=8.4Hz), 7.25 (2H, d, J=7.4Hz), 7.35-7.59 (9H, m).

IR(KBr) ν: 2936, 1651, 1520cm⁻¹.

Anal. for C₃₁H₃₃N₃O₃:

Calcd. C, 77.15; H, 7.10; N, 5.80.

Found C, 76.95; H, 7.34; N, 5.69.

Working Example 146 (Production of Compound 146)

To a solution of 7-(3-pyridyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetra-hydropyran-4-yl)aminomethyl)aniline (0.12g) and triethylamine (0.16ml) in dimethylformamide (50ml) was added diethyl cyano-phosphate (0.1ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (methanol/ethyl acetate/triethylamine) to give crude crystals, which were recrystallized from ethanol-hexane to give 7-(3-pyridyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)-methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 146) (0.06g) as colorless crystals.

mp 158-159°C.

¹H-NMR(δ ppm, CDCl₃): 1.64-1.71 (4H, m), 2.23 (3H, s),

- 2.65-2.75 (1H, m), 3.11 (2H, t, J=4.8Hz), 3.37 (2H, dt, J=2.4, 11.0Hz), 3.60 (2H, s), 4.01-4.07 (2H, m), 4.38 (2H, t, J=4.8Hz), 7.12 (1H, d, J=8.4Hz), 7.31-7.40 (3H, m), 7.44-7.58 (4H, m), 7.66 (1H, br), 7.84 (1H, d, J=7.6Hz),
5 8.58 (1H, d, J=4.8Hz), 8.82 (1H, d, J=2.2Hz).

IR(KBr) ν : 2949, 2845, 1661 cm^{-1} .

Anal. for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$:

Calcd. C, 72.78; H, 6.74; N, 8.78.

Found C, 72.72; H, 6.72; N, 8.95.

10 Working Example 147 (Production of Compound 147)

- To a solution of 7-(4-pyridyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.12g) and triethylamine (0.16ml) in dimethylformamide (50ml) was
15 added diethyl cyano-phosphate (0.1ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (methanol/ethyl acetate/triethylamine) to give crude
20 crystals, which were recrystallized from ethanol-hexane to give 7-(4-pyridyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 147) (0.07g) as pale brown crystals.
mp 186-187°C.

- 25 $^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.67-1.73 (4H, m), 2.23 (3H, s), 2.60-2.75 (1H, m), 3.11 (2H, t, J=4.6Hz), 3.37 (2H, dt, J=3.0, 11.0Hz), 3.60 (2H, s), 4.01-4.07 (2H, m), 4.38 (2H, t, J=4.6Hz), 7.12 (1H, d, J=8.0Hz), 7.34 (2H, d, J=8.4Hz), 7.45-7.51 (3H, m), 7.55-7.59 (3H, m), 7.82 (1H, br), 8.64
30 (2H, d, J=5.8Hz).

IR(KBr) ν : 2948, 1659 cm^{-1} .

Anal. for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$:

Calcd. C, 72.78; H, 6.74; N, 8.78.

Found C, 72.64; H, 6.51; N, 8.85.

35 Working Example 148 (Production of Compound 148)

To a solution of 7-(2-furyl)-2,3-dihydro-1-

benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.15g) and triethylamine (0.25ml) in dimethylformamide (10ml) was added diethyl cyanophosphate (0.13ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (methanol/ethyl acetate/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(2-furyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 148) (0.1g) as brown crystals.

mp 166-167°C(dec.).

¹H-NMR(δ ppm, CDCl₃): 1.64-1.78 (4H, m), 2.22 (3H, s), 2.60-2.75 (1H, m), 3.06 (2H, t, J=4.6Hz), 3.37 (2H, dt, J=3.0, 11.1Hz), 3.59 (2H, s), 4.02-4.07 (2H, m), 4.33 (2H, t, J=4.6Hz), 6.46 (1H, dd, J=1.8, 3.3Hz), 6.56 (1H, d, J=3.3Hz), 7.01 (2H, d, J=8.4Hz), 7.21 (1H, s), 7.32 (2H, d, J=8.6Hz), 7.44 (1H, d, J=1.8Hz), 7.50-7.62 (4H, m), 7.73 (1H, s). IR(KBr) ν: 2951, 1659cm⁻¹.

Anal. for C₂₈H₃₀N₂O₄·0.5H₂O:

Calcd. C, 71.93; H, 6.68; N, 5.99.

Found C, 71.97; H, 6.52; N, 6.08.

25 Working Example 149 (Production of Compound 149)

To a solution of 7-(4-dimethylaminophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.11g) and triethylamine (0.2ml) in dimethylformamide (15ml) was added diethyl cyano-phosphate (0.11ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (methanol/ethyl acetate/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(4-dimethylaminophenyl)-N-(4-

((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-
2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 149)
(0.07g) as pale brown crystals.

mp 208-209°C(dec.).

- 5 ¹H-NMR(δ ppm, CDCl₃): 1.63-1.78 (4H, m), 2.20 (3H, s),
2.59-2.70 (1H, m), 2.98 (6H, s), 3.04 (2H, t, J=4.5Hz), 3.36
(2H, dt, J=2.6, 11.0Hz), 3.56 (2H, s), 4.00-4.06 (2H, m),
4.31 (2H, t, J=4.5Hz), 6.78 (2H, d, J=8.8Hz), 7.01 (1H, d,
J=8.0Hz), 7.24-7.31 (3H, m), 7.39-7.46 (4H, m), 7.55 (2H,
10 d, J=8.4Hz), 7.79 (1H, s).

IR(KBr) ν: 2949, 2845, 1659cm⁻¹.

Anal. for C₂₂H₂₇N₃O₃·0.3H₂O:

Calcd. C, 74.33; H, 7.33; N, 8.13.

Found C, 74.11; H, 7.22; N, 8.21.

- 15 Working Example 150 (Production of Compound 150)

To a solution of 7-(4-(pyrrolidin-1-yl)phenyl)-
2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-
(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline
(0.1g) and 1-hydroxybenzotriazole (0.07g) in dimethyl-
20 formamide (10ml) was added 1-ethyl-3-(3-dimethylamino-
propyl)carbodiimide hydro-chloride (0.13g) under ice-
cooling, and the mixture was stirred under nitrogen
atmosphere at room temperature for 3 hours. To the mixture
were added 4-dimethylaminopyridine (catalytic amount) and
25 1,8-diazabicyclo[5.4.0]-7-undecene (0.2ml), and the
mixture was stirred over night. The solvent was evaporated,
and the residue was purified with silica gel column
(methanol/ethyl acetate/triethylamine) to give crude
crystals, which were recrystallized from ethanol-hexane to
30 give 7-(4-(pyrrolidin-1-yl)phenyl)-N-(4-((N-tetrahydro-
pyran-4-yl-N-methylamino)-methyl)phenyl)-2,3-dihydro-1-
benzoxepine-4-carboxamide (Compound 150) (0.08g) as
colorless crystals.

mp 210-211°C.

- 35 ¹H-NMR(δ ppm, CDCl₃): 1.69-1.78 (8H, m), 1.99-2.06 (4H, m),
2.21 (3H, s), 2.55-2.70 (1H, m), 3.07 (2H, t, J=4.5Hz),

3.30-3.38 (4H, m), 3.38-3.57 (2H, m), 3.57 (2H, s), 4.01-4.06 (2H, m), 4.35 (2H, t, J=4.5Hz), 6.63 (2H, d, J=8.8Hz), 7.02 (1H, d, J=8.4Hz), 7.31 (2H, d, J=8.4Hz), 7.40-7.48 (4H, m), 7.54 (2H, d, J=8.4Hz), 7.61 (1H, s).

5 IR(KBr) ν : 2951, 2841, 1653cm⁻¹.

Anal. for C₂₄H₂₉N₃O₃:

Calcd. C, 75.95; H, 7.31; N, 7.81.

Found C, 75.70; H, 7.10; N, 7.83.

Working Example 151 (Production of Compound 151)

10 To a solution of 7-(4-piperidinophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.1g) and 1-hydroxy-benzotriazole (0.07g) in dimethylformamide (10ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
15 hydrochloride (0.13g) under ice-cooling. Under nitrogen atmosphere, the mixture was warmed to room temperature. To the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.18ml), and the mixture was stirred over night. The solvent was evaporated, and to the
20 residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized
25 from ethyl acetate-hexane to give 7-(4-piperidino-phenyl)-N-(4-((N-methyl-N-tetrahydro-pyran-4-yl)amino)-methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 151) (0.18g) as colorless crystals.
mp 197-198°C.

30 ¹H-NMR(δ ppm, CDCl₃): 1.58-1.70 (2H, m), 1.70-1.73 (4H, m), 2.21 (3H, s), 2.55-2.70 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.18-3.23 (4H, m), 3.37 (2H, dt, J=2.4, 11.0Hz), 3.57 (2H, s), 4.01-4.07 (2H, m), 4.35 (2H, t, J=4.6Hz), 6.63 (2H, d, J=8.8Hz), 6.97-7.05 (3H, m), 7.31 (2H, d, J=8.4Hz),
35 7.43-7.57 (7H, m).

IR(KBr) ν : 2938, 2847, 1651cm⁻¹.

Anal. for $C_{33}H_{41}N_3O_3 \cdot 0.5H_2O$:

Calcd. C, 74.97; H, 7.55; N, 7.49.

Found C, 75.26; H, 7.53; N, 7.63.

Working Example 152 (Production of Compound 152)

5 To a solution of 7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.1g) and 1-hydroxybenzotriazole (0.06g) in dimethylformamide (15ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
10 hydrochloride (0.12g) under ice-cooling. Under nitrogen atmosphere, the mixture was warmed to room temperature. To the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.18ml), and the mixture was stirred over night. The mixture was poured into water and
15 was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give
20 N-(4-((N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)-phenyl)-7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 152) (0.17g) as pale brown crystals.

mp 238-239°C(dec.).

25 1H -NMR(δ ppm, $CDCl_3$): 1.58-1.77 (4H, m), 2.21 (3H, s), 2.55-2.75 (1H, m), 3.08 (2H, t, $J=4.6Hz$), 3.19-3.24 (4H, m), 3.37 (2H, dt, $J=3.0, 11.3Hz$), 3.57 (2H, s), 3.87-3.91 (4H, m), 4.01-4.11 (2H, m), 4.36 (2H, t, $J=4.6Hz$), 6.98 (2H, d, $J=9.0Hz$), 7.05 (1H, d, $J=8.4Hz$), 7.27-7.34 (3H, m),
30 7.42-7.57 (6H, m).

IR(KBr) ν : 2961, 2847, 1660 cm^{-1} .

Anal. for $C_{34}H_{43}N_3O_4 \cdot 0.5H_2O$:

Calcd. C, 72.57; H, 7.16; N, 7.47.

Found C, 72.79; H, 7.08; N, 7.35.

35 Working Example 153 (Production of Compound 153)

To a solution of 7-(4-(1-imidazolyl)phenyl)-2,3-

- dihydro-1-benzoxepine-4-carboxylic acid (0.13g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.11g) and 1-hydroxybenzotriazole (0.07g) in dimethylformamide (20ml) was added 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (0.13g) under ice-cooling. Under nitrogen atmosphere, the mixture was warmed to room temperature. To the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.2ml), and the mixture was stirred over night. The solvent was evaporated, and the residue was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol-hexane to give 7-(4-(1-imidazolyl)phenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 153) (0.11g) as pale yellow crystals.
- mp 194-195°C.
- ¹H-NMR(δ ppm, CDCl₃): 1.63-1.80 (4H, m), 2.21 (3H, s), 2.59-2.70 (1H, m), 3.10 (2H, t, J=4.6Hz), 3.37 (2H, dt, J=2.6, 11.8Hz), 3.58 (2H, s), 4.00-4.08 (2H, m), 4.39 (2H, t, J=4.6Hz), 7.11 (1H, d, J=8.2Hz), 7.23-7.24 (1H, m), 7.30-7.34 (4H, m), 7.42-7.46 (3H, m), 7.51 (1H, s), 7.57 (2H, d, J=8.6Hz), 7.65 (2H, d, J=8.6Hz), 7.84 (1H, br), 7.91 (1H, s).
- IR(KBr) ν: 2949, 2843, 1651cm⁻¹.
- Anal. for C₃₃H₃₃N₅O₃·0.2H₂O:
Calcd. C, 73.64; H, 6.44; N, 10.41.
Found C, 73.63; H, 6.23; N, 10.46.
- Working Example 154 (Production of Compound 154)
- To a solution of 7-(4-dimethylaminophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.1g), 1-(4-aminobenzyl)phosphorinane-1-oxide (0.08g) and 1-

hydroxybenzotriazole (0.05g) in dimethylformamide (7ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.1g) under ice-cooling. Under nitrogen atmosphere, the mixture was warmed to room temperature. To
5 the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.15ml), and the mixture was stirred over night. The solvent was evaporated, and the residue was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution,
10 and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol-hexane to give 7-(4-dimethyl-
15 aminophenyl)-N-(4-((1-oxophosphorinan-1-yl)methyl)-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 154) (0.12g) as colorless crystals.
mp 293-294°C(dec.).

¹H-NMR(δ ppm, CDCl₃): 1.35-1.55 (2H, m), 1.60-1.75 (6H, m),
20 1.75-2.05 (2H, m), 3.00 (6H, s), 3.09 (2H, t, J=4.7Hz), 3.13 (2H, d, J=13.6Hz), 4.35 (2H, t, J=4.7Hz), 6.80 (2H, d, J=8.8Hz), 7.03 (1H, d, J=8.4Hz), 7.21-7.27 (3H, m), 7.41-7.51 (4H, m), 7.60 (2H, d, J=8.2Hz), 8.24 (1H, br).
IR(KBr) ν: 2940, 1665cm⁻¹.

25 Anal. for C₃₁H₃₃N₂O₃P:
Calcd. C, 72.35; H, 6.86; N, 5.44.
Found C, 72.00; H, 6.84; N, 5.45.

Working Example 155 (Production of Compound 155)

To a solution of 7-(4-dimethylaminophenyl)-N-(4-
30 ((1-oxophosphorinan-1-yl)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) in ethanol was added 4N hydrochloric acid-ethyl acetate (0.2ml) under ice-cooling. The solvent was evaporated, and the residue was crystallized from ethanol and diethylether to give 7-(4-dimethylamino-
35 phenyl)-N-(4-((1-oxophosphorinan-1-yl)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide hydrochloride

(Compound 155) (0.1g) as colorless crystals.
mp 162-163°C.

¹H-NMR(δ ppm, DMSO-d₆): 1.40-1.50 (2H, m), 1.50-1.90 (8H, m),
2.99 (2H, br), 3.04 (6H, s), 3.16 (2H, d, J=13.6Hz), 4.30
5 (2H, br), 7.05 (1H, d, J=8.8Hz), 7.20-7.25 (4H, m), 7.35
(1H, s), 7.54 (1H, dd, J=2.2, 8.2, 8.8Hz), 7.63-7.69 (4H,
m), 7.74 (1H, d, J=2.2Hz), 9.97 (1H, s).

Anal. for C₃₁H₃₃N₂O₃P·HCl·2H₂O:

Calcd. C, 63.42; H, 6.87; N, 4.77.

10 Found C, 63.45; H, 6.99; N, 4.39.

Working Example 156 (Production of Compound 156)

In methanol (100ml) and ethyl acetate (150ml) was
dissolved N-(4-(1-(tert-butoxycarbonyl)piperidin-2-
ylcarbonyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-
15 benzoxepine-4-carboxamide (1.0g), and to the mixture was
added hydrochloric acid (17ml). The mixture was stirred at
room temperature for 2 hours, concentrated and neutralized
with sodium hydrogen carbonate solution. The mixture was
extracted with ethyl acetate. The organic layer was washed
20 with water and saturated sodium chloride solution, and dried
with anhydrous magnesium sulfate. Under reduced pressure,
the solvent was evaporated to give crude crystals, which
were recrystallized from ethanol-ethyl acetate-hexane to
give N-(4-(piperidin-2-ylcarbonyl)phenyl)-7-(4-methyl-
25 phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 156) (0.6g) as colorless crystals.
mp 195-196°C(dec.).

¹H-NMR(δ ppm, CDCl₃): 1.26-1.49 (2H, m), 1.50-1.70 (2H, m),
1.87-1.94 (2H, m), 2.39 (3H, s), 2.79 (1H, t, J=12.0Hz),
30 3.08 (2H, t, J=4.4Hz), 3.26 (1H, d, J=12.0Hz), 4.26-4.37
(3H, m), 7.06 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.4Hz), 7.30
(1H, s), 7.43-7.53 (4H, m), 7.71 (2H, d, J=8.8Hz), 7.90-7.95
(3H, m).

IR(KBr) ν: 2934, 1674cm⁻¹.

35 Anal. for C₃₀H₃₀N₂O₃·0.3H₂O:

Calcd. C, 76.34; H, 6.53; N, 5.94.

Found C,76.35; H,6.44; N,5.88.

Working Example 157 (Production of Compound 157)

In dichloromethane (35ml) was dissolved N-(4-(piperidin-2-ylcarbonyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.3g), and to the solution were added methyl iodide (0.08ml) and diisopropylethylamine (0.17ml). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-(1-methylpiperidin-2-ylcarbonyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 157) (0.17g) as colorless crystals.

mp 162-163.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.27-1.45 (2H, m), 1.50-1.90 (4H, m), 2.04-2.20 (1H, m), 2.21 (3H, s), 2.39 (3H, s), 3.00-3.05 (1H, m), 3.08 (2H, t, $J=4.6\text{Hz}$), 3.48 (1H, d, $J=7.6\text{Hz}$), 4.36 (2H, t, $J=4.6\text{Hz}$), 7.06 (1H, d, $J=8.0\text{Hz}$), 7.25 (2H, d, $J=12.4\text{Hz}$), 7.43-7.51 (4H, m), 7.69 (2H, d, $J=8.8\text{Hz}$), 7.81 (1H, s), 8.18 (2H, d, $J=8.4\text{Hz}$).

IR(KBr) ν : 2940, 1667 cm^{-1} .

Anal. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_3$:

Calcd. C,77.47; H,6.71; N,5.83.

Found C,77.22; H,6.71; N,5.63.

Working Example 158 (Production of Compound 158)

In methanol (40ml) was dissolved N-(4-(1-methylpiperidin-2-ylcarbonyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.1g) under ice-cooling, and to the mixture was added sodium boron hydride (10mg). The mixture was stirred for 15 minutes, and to the

mixture was added water. The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol-ethyl acetate-hexane to give N-(4-(hydroxy(1-methylpiperidin-2-yl)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 158) (0.07g) as colorless crystals. mp 195-196.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.95-1.05 (2H, m), 1.25-1.40 (2H, m), 2.04-2.30 (4H, m), 2.39 (3H, s), 2.50 (3H, s), 2.95-3.01 (1H, m), 3.08 (2H, t, $J=4.6\text{Hz}$), 4.36 (2H, t, $J=4.6\text{Hz}$), 5.16 (1H, d, $J=3.0\text{Hz}$), 7.06 (1H, d, $J=8.4\text{Hz}$), 7.24 (2H, d, $J=8.0\text{Hz}$), 7.33 (2H, d, $J=8.4\text{Hz}$), 7.43-7.52 (4H, m), 7.56 (2H, d, $J=8.4\text{Hz}$), 7.61 (1H, s).
IR(KBr) ν : 3287, 2938, 1647 cm^{-1} .

Anal. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_3 \cdot 0.6\text{H}_2\text{O}$:

Calcd. C, 75.46; H, 7.19; N, 5.68.

Found C, 75.36; H, 7.33; N, 5.76.

Working Example 159 (Production of Compound 159)

Under nitrogen atmosphere, oxalyl chloride (0.31ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-benzoxepine-4-carboxylic acid (0.65g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (15ml). To the solution were added triethylamine (0.65ml) and 2-(4-aminophenyl)pyridine (J. Chem. Soc., p.1511, 1960) (0.44g) at 0°C , and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. Precipitated crystal was collected by filtration to give

- N-[4-(2-pyridyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 159) (185.9mg) as colorless crystals. The mother liquor was concentrated and recrystallized from ethyl acetate-tetrahydrofuran to give
- 5 N-[4-(2-pyridyl)-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 159) (0.58g) as pale yellow crystals.
m.p. 228-229°C
- ¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.09 (2H, t, J=4.4 Hz), 4.36 (2H, t, J=4.4 Hz), 7.06 (1H, d, J=8.2 Hz), 7.16-7.32 (4H, m), 7.42-7.56 (4H, m), 7.68-7.82 (5H, m), 8.02 (2H, dd, J=8.8, 2.0 Hz), 8.65-8.73 (1H, dt, J=4.8, 1.4 Hz). IR (KBr) 3338, 1645, 1593, 1516, 1493, 1466, 1435, 1323, 1248, 810, 777 cm⁻¹
- 15 Elemental Analysis for C₂₉H₂₄N₂O₂
Calcd. C, 80.53 ; H, 5.59 ; N, 6.48 :
Found. C, 80.46 ; H, 5.62 ; N, 6.46.
- Working Example 160 (Production of Compound 160)
- To a suspension of N-[4-(2-pyridyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (400mg) in dichloromethane (10ml) was added 3-chloro-perbenzoic acid (70%, 0.25g) at 0°C, and the mixture was stirred at room temperature for 70 hours. To the mixture was added sodium thiosulfate solution, and the mixture was
- 25 stirred for minutes. The mixture was extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, and dried with magnesium sulfate. The mixture was concentrated, purified with column
- 30 chromatography (ethanol/ethyl acetate=1:1) to give crystals, which were dissolved in chloroform. The mixture was concentrated, and to the residue was added ethanol. Precipitated crystal was collected by filtration to give crystals, which were washed with ethanol to give N-[4-
- 35 (1-oxidopyridin-2-yl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 160) (60mg)

as colorless crystals.

m.p. 254 °C(dec.)

¹H-NMR (200MHz, CDCl₃) δ 2.40 (3H, s), 3.06 (2H, t, J=4.4 Hz), 4.36 (2H, t, J=4.4 Hz), 7.00-7.14 (2H, m), 7.16-7.30 (4H, m), 7.38-7.51 (5H, m), 7.67 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.8 Hz), 8.19 (1H, d, J=7.0 Hz), 8.38-8.48 (1H, m).

IR (KBr) 3334, 3039, 1653, 1487, 1240, 814, 760 cm⁻¹

Elemental Analysis for C₂₃H₂₄N₂O₃ · 0.5H₂O

Calcd. C, 76.13 ; H, 5.51 ; N, 6.12 :

Found. C, 75.82 ; H, 5.27 ; N, 6.18.

Working Example 161 (Production of Compound 161)

Under nitrogen atmosphere, oxalyl chloride (0.19ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.40g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (6ml). To the solution were added triethylamine (0.40ml) and a solution of 2-(4-aminobenzyl)pyridine (0.29g) in tetrahydrofuran (5ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from ethyl acetate to give N-[4-(2-pyridylmethyl)-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 161) (303mg) as colorless crystals.

m.p. 189-190°C

¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.06 (2H, t, J=4.6 Hz), 4.14 (2H, s), 4.35 (2H, t, J=4.6 Hz), 7.03-7.16 (3H, m), 7.18-7.31 (5H, m), 7.40-7.64 (8H, m), 8.52-8.58 (1H, m).

IR (KBr) 3338, 1645, 1510, 1493, 1414, 1313, 1252, 1234,

816, 750 cm^{-1}

Elemental Analysis for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2$

Calcd. C, 80.69 ; H, 5.87 ; N, 6.27 :

Found. C, 80.63 ; H, 5.80 ; N, 6.37.

5 Working Example 162 (Production of Compound 162)

To a solution of N-[4-(2-pyridylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (200mg) in tetrahydrofuran (10ml) was added 3-chloro-perbenzoic acid (70%, 0.18g) at 0°C , and the mixture was stirred at room temperature for 17 hours. To the reaction mixture was added sodium thio-sulfate solution, and the mixture was stirred for a few minutes. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated to give crystals, which were collected by filtration and was recrystallized from ethanol to give N-[4-(1-oxidopyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 162) (124mg) as colorless crystals. m.p. $188-190^\circ\text{C}$

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 2.39 (3H, s), 3.09 (2H, t, $J=4.6$ Hz), 4.24 (2H, s), 4.36 (2H, t, $J=4.6$ Hz), 6.90-7.01 (1H, m), 7.06 (1H, d, $J=8.4$ Hz), 7.11-7.16 (2H, m), 7.22-7.29 (5H, m), 7.43-7.51 (4H, m), 7.54-7.76 (3H, m), 8.24-8.31 (1H, m).

IR (KBr) 3319, 1666, 1601, 1517, 1491, 1412, 1319, 1246, 813 cm^{-1}

Elemental Analysis for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2 \cdot 0.3\text{H}_2\text{O}$

30 Calcd. C, 77.00 ; H, 5.73 ; N, 5.99 :

Found. C, 76.98 ; H, 5.59 ; N, 6.10.

Working Example 163 (Production of Compound 163)

Under nitrogen atmosphere, oxalyl chloride (0.07ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (144.8mg) in tetrahydrofuran (10ml) at room temperature. To the mixture

was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml).

To the solution were added triethylamine (0.14ml) and a solution of 4-aminobenzyl-diethylphosphine oxide (120mg) in tetrahydrofuran (5ml) at 0°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from ethanol-tetrahydrofuran to give N-(4-diethylphosphoryl-methylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 163) (157mg) as colorless crystals.

m.p. 240-241°C

¹H-NMR (200MHz, CDCl₃) δ 1.13 (6H, dt, J=16.4, 8.0 Hz), 1.53-1.72 (4H, m), 2.39 (3H, s), 3.06-3.13 (4H, m), 4.36 (2H, t, J=4.8 Hz), 7.06 (1H, d, J=8.4 Hz), 7.22-7.27 (5H, m), 7.44-7.52 (4H, m), 7.58 (2H, d, J=8.4 Hz), 7.98 (1H, s).

IR (KBr) 3263, 1653, 1599, 1516, 1491, 1410, 1319, 1250, 1173, 1132, 843, 808 cm⁻¹

Elemental Analysis for C₂₂H₂₂NO₂P

Calcd. C, 73.55 ; H, 6.81 ; N, 2.96 ; P, 6.54 ;

Found. C, 73.23 ; H, 6.64 ; N, 3.01 ; P, 6.63.

Working Example 164 (Production of Compound 164)

Under nitrogen atmosphere, oxalyl chloride (0.28ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.60g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.60ml) and 3-(4-aminophenyl)pyridine (J. Chem. Soc., p.1511, 1960)

- (0.40g) at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from ethanol to give N-[4-(3-pyridyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 164) (750mg) as yellow crystals.
- m.p. 214-216°C
- ¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.07-3.11 (2H, m), 4.34-4.39 (2H, m), 7.06 (1H, d, J=8.2 Hz), 7.18-7.63 (10H, m), 7.71-7.90 (4H, m), 8.57-8.59 (1H, m), 8.85 (1H, d, J=1.8 Hz).
- IR (KBr) 3313, 1666, 1524, 1493, 1321, 1244, 808 cm⁻¹
- Elemental Analysis for C₂₂H₂₀N₂O₂ · 0.2H₂O
- Calcd. C, 79.87 ; H, 5.64 ; N, 6.42 ;
- Found. C, 80.00 ; H, 5.59 ; N, 6.00.
- Working Example 165 (Production of Compound 165)
- To a solution of N-[4-(3-pyridyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (400mg) in tetrahydrofuran (50ml) was added 3-chloroperbenzoic acid (70%, 0.34g) at 0°C, and the mixture was stirred at room temperature for 68 hours. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes and extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:1), and recrystallized from ethanol-chloroform to give N-[4-(1-oxidopyridin-3-yl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 165) (216mg) as pale yellow crystals.
- m.p. 262°C (dec.)

¹H-NMR (200MHz, CDCl₃) δ 2.40 (3H, s), 3.10 (2H, t, J=4.4 Hz), 4.38 (2H, t, J=4.4 Hz), 7.07 (1H, d, J=8.4 Hz), 7.23-7.36 (4H, m), 7.42-7.58 (7H, m), 7.76 (2H, dd, J=8.8, 2.0 Hz), 7.88 (1H, br s), 8.16-8.20 (1H, m), 8.43-8.47 (1H, m).

5 IR (KBr) 3313, 1655, 1599, 1525, 1491, 1244, 1203, 814 cm⁻¹

Elemental Analysis for C₂₂H₂₁N₃O₃ · 0.1H₂O

Calcd. C, 77.35 ; H, 5.42 ; N, 6.22 :

Found. C, 77.13 ; H, 5.28 ; N, 6.21.

Working Example 166 (Production of Compound 166)

10 Under nitrogen atmosphere, oxalyl chloride (0.19ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.40g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred
15 for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added at 0°C triethylamine (0.40ml) and (4-aminophenyl)-(2-pyridyl)methanol (0.31g), and the mixture was stirred at room temperature for 18 hours.
20 The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from ethanol-ethyl acetate
25 to give N-[4-[hydroxy(2-pyridyl)-methyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 166) (549mg) as pale yellow crystals.
m.p. 215-217°C

30 ¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.06 (2H, t, J=4.4 Hz), 4.34 (2H, t, J=4.4 Hz), 5.26-5.38 (1H, m), 5.70-5.78 (1H, m), 7.03-7.27 (6H, m), 7.33-7.79 (10H, m), 8.57 (1H, d, J=4.8 Hz).

IR (KBr) 3392, 1651, 1537, 1514, 1493, 1319, 1248 cm⁻¹

Elemental Analysis for C₃₀H₂₆N₂O₃ · 0.2H₂O

35 Calcd. C, 77.30 ; H, 5.71 ; N, 6.01 :

Found. C, 77.21 ; H, 5.75 ; N, 5.86.

Working Example 167 (Production of Compound 167)

To a solution of N-[4-[hydroxy(2-pyridyl)methyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (351.3mg) in tetrahydrofuran (20ml) was added
5 3-chloroperbenzoic acid (70%, 0.28g) at 0°C, and the mixture was stirred at room temperature for 16 hours. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes. The mixture was extracted with ethyl acetate. The organic layer was washed
10 with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol-diethylether=1:1), and recrystallized from ethanol to give N-[4-[hydroxy(1-
15 oxidopyridin-2-yl)methyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 167) (184mg) as colorless crystals.

m.p. 208-210°C

¹H-NMR (200MHz, CDCl₃) δ 2.40 (3H, s), 3.09 (2H, t, J=4.4 Hz), 4.37 (2H, t, J=4.5 Hz), 6.07 (1H, d, J=4.5 Hz), 6.41 (1H, d, J=4.6 Hz), 6.93-6.98 (1H, m), 7.06 (1H, d, J=8.4 Hz), 7.20-7.31 (5H, m), 7.41-7.55 (6H, m), 7.65 (2H, d, J=8.8 Hz), 7.73 (1H, br s), 8.24-8.28 (1H, m).

IR (KBr) 3427, 1645, 1599, 1531, 1514, 1491, 1317, 1263 cm⁻¹

25 Elemental Analysis for C₂₆H₂₆N₂O₄ · 0.1H₂O

Calcd. C, 75.01 ; H, 5.50 ; N, 5.83 ;

Found. C, 74.96 ; H, 5.36 ; N, 5.73.

Working Example 168 (Production of Compound 168)

Under nitrogen atmosphere, oxalyl chloride (0.2ml) was
30 added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (400mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour.

Under reduced pressure, the solvent was evaporated, and the
35 residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.4ml) and 4-amino-

benzyl dipropylphosphine oxide (0.38g) at 0°C, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:5), and recrystallized from ethanol to give N-(4-dipropylphosphorylmethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 168) (456mg) as colorless crystals.

m.p. 219-220°C

¹H-NMR (200MHz, CDCl₃) δ 0.84-0.98 (6H, m), 1.41-1.63 (8H, m), 2.39 (3H, s), 3.02 (2H, d, J=13.2 Hz), 3.09 (2H, t, J=4.4 Hz), 4.35 (2H, t, J=4.4 Hz), 7.06 (1H, d, J=8.0 Hz), 7.13-7.29 (5H, m), 7.44-7.48 (3H, m), 7.53 (1H, d, J=2.2 Hz), 7.61 (2H, d, J=8.0 Hz), 8.64 (1H, s).

IR (KBr) 3386, 2960, 1653, 1518, 1491, 1319, 1248, 1185, 1128, 849 cm⁻¹

Elemental Analysis for C₂₁H₂₆NO₃P · 0.3H₂O

Calcd. C, 73.44 ; H, 7.28 ; N, 2.76 ; P, 6.11 ;

Found. C, 73.35 ; H, 7.40 ; N, 2.62 ; P, 6.35.

Working Example 169 (Production of Compound 169)

Under nitrogen atmosphere, oxalyl chloride (0.17ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (350mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.35ml) and (4-aminophenyl)(3-methoxy-pyridin-2-yl)methanol (316mg) at 0°C, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was

extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate), and recrystallized from tetrahydrofuran-hexane to give N-[4-[hydroxy(3-methoxy-pyridin-2-yl)methyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 169) (509mg) as colorless crystals. m.p. 232-233°C

¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.05 (2H, t, J=4.8 Hz), 3.77 (3H, s), 4.34 (2H, t, J=4.8 Hz), 5.51 (1H, d, J=6.8 Hz), 5.93 (1H, d, J=6.8 Hz), 7.05 (1H, d, J=8.0 Hz), 7.10-7.26 (5H, m), 7.34-7.54 (9H, m), 8.18 (1H, d, J=5.2 Hz).

IR (KBr) 3354, 1651, 1518, 1491, 1412, 1311, 1279, 1240, 1211, 1022, 816 cm⁻¹

Elemental Analysis for C₃₁H₂₈N₂O₄

Calcd. C, 75.59 ; H, 5.73 ; N, 5.69 ;

Found. C, 75.47 ; H, 5.61 ; N, 5.70.

Working Example 170 (Production of Compound 170)

To a solution of N-[4-[hydroxy-(3-methoxypyridin-2-yl)methyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (350mg) in tetrahydrofuran (30ml) was added 3-chloroperbenzoic acid (70%, 0.26g) at 0°C, and the mixture was stirred at room temperature for 64 hours. To the mixture was added sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate→ ethanol/ethyl acetate=1:4) recrystallized from tetrahydrofuran-hexane to give N-[4-[hydroxy(3-methoxy-1-oxidopyridin-2-yl)methyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 170) (168mg) as colorless crystals.

m.p. 242°C (dec.)

¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.06 (2H, t, J=4.4 Hz), 3.97 (3H, s), 4.35 (2H, t, J=4.4 Hz), 6.34 (1H, d, J=11.4 Hz), 6.97 (1H, d, J=7.8 Hz), 7.05 (1H, d, J=8.2 Hz), 7.14-7.27 (4H, m), 7.42-7.53 (8H, m), 7.61 (1H, br s), 7.84 (1H, d, J=6.6 Hz), 7.87 (1H, d, J=11.2 Hz).

IR (KBr) 3493, 3294, 2953, 1657, 1601, 1516, 1493, 1323, 1207, 1184, 1088, 1043, 817 cm⁻¹

Elemental Analysis for C₃₁H₂₈N₂O₅ · 0.2H₂O

10 Calcd. C, 72.70 ; H, 5.59 ; N, 5.47 ;

Found. C, 72.53 ; H, 5.64 ; N, 5.36.

Working Example 171 (Production of Compound 171)

Under nitrogen atmosphere, oxalyl chloride (0.12ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (250mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.25ml) and 1-(4-aminobenzyl)-phosphorane-1-oxide (204.8mg) at 0°C, and the mixture was stirred at room temperature 18 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution, concentrated and recrystallized from ethanol to give N-(4-(tetramethylene)phosphoryl-methylphenyl)-7-(4-methylphenyl)-2,3-dihydro-benzoxepine-4-carboxamide (Compound 171) (316mg) as colorless crystals.

m.p. 273-275°C

¹H-NMR (200MHz, CDCl₃) δ 1.43-1.97 (8H, m), 2.40 (3H, s), 3.09 (2H, t, J=4.4 Hz), 3.20 (2H, d, J=14.4 Hz), 4.40 (2H, t, J=4.4 Hz), 7.06 (1H, d, J=8.4 Hz), 7.18-7.29 (5H, m), 7.44-7.54 (4H, m), 7.60 (2H, d, J=8.0 Hz), 8.12-8.23 (1H, m).

IR (KBr) 3223, 2952, 1653, 1518, 1491, 1321, 1254, 1186, 810 cm^{-1}

Elemental Analysis for $\text{C}_{22}\text{H}_{20}\text{NO}_3\text{P}$

Calcd. C, 73.87 ; H, 6.41 ; N, 2.97 ; P, 6.57 :

5 Found. C, 73.79 ; H, 6.33 ; N, 3.00 ; P, 6.59.

Working Example 172 (Production of Compound 172)

Under nitrogen atmosphere, oxalyl chloride (0.47ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (1.0g) in 10 tetrahydrofuran (20ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml) at 0°C . To the solution were added triethylamine (1.0ml) and 15 2-(4-aminobenzyl)-3-methoxymethoxypyridine (0.96g), and the mixture was stirred at room temperature for 4 hours.

The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium 20 chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=2:1) to give N-[4-(3-methoxymethoxy-pyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide 25 (Compound 172) (1.63g) as orange crystals.

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 2.39 (3H, s), 3.03 (2H, t, $J=4.4$ Hz), 3.37 (3H, s), 4.18 (2H, s), 4.32 (2H, t, $J=4.4$ Hz), 5.17 (2H, s), 7.03 (1H, d, $J=8.0$ Hz), 7.10 (1H, dd, $J=8.4$, 4.8 Hz), 7.19-7.51 (12H, m), 7.62 (1H, br s), 8.20 (1H, dd, 30 $J=4.8$, 1.2 Hz).

IR (KBr) 3275, 2945, 1659, 1516, 1444, 1406, 1491, 1313, 1240, 1153, 982. 814 cm^{-1}

Working Example 173 (Production of Compound 173)

To a solution of N-[4-(3-methoxymethoxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1- 35 benzoxepine-4-carboxamide (300mg) in tetrahydrofuran

(10ml) was added 3-chloroperbenzoic acid (70%, 0.22g) at 0°C, and the mixture was stirred at room temperature for 18 hours. To the mixture was added sodium thiosulfate, and the mixture was stirred for a few minutes. The mixture was
5 extracted with ethyl acetate, and the organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column
10 chromatography (ethanol/ethyl acetate=1:15→1:10), and recrystallized from ethanol to give N-[4-(1-oxido-3-methoxymethoxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 173) (203mg) as colorless crystals.

15 m.p. 206-208°C

¹H-NMR (200MHz, CDCl₃) δ 2.39 (3H, s), 3.06 (2H, t, J=4.6 Hz), 3.44 (3H, s), 4.35 (2H, t, J=4.6 Hz), 4.37 (2H, s), 5.24 (2H, s), 6.96-7.08 (3H, m), 7.19-7.27 (4H, m), 7.38-7.52 (7H, m), 7.62 (1H, br s), 7.99 (1H, dd, J=5.0, 2.2 Hz).

20 IR (KBr) 3305, 1653, 1601, 1516, 1491, 1321, 1244, 1053, 818 cm⁻¹

Elemental Analysis for C₂₂H₂₀N₂O₃ · 0.2H₂O

Calcd. C, 73.04 ; H, 5.82 ; N, 5.32 ;

Found. C, 72.96 ; H, 5.72 ; N, 5.30.

25 Working Example 174 (Production of Compound 174)

To a solution of N-[4-(3-methoxymethoxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (1.00g) in ethanol(20ml) was added concentrated hydrochloric acid (5.0ml), and the
30 mixture was stirred at room temperature for 4 days. To the mixture was added saturated sodium bicarbonate solution at 0°C to make the solution pH 6-7, and precipitated crystal was collected by filtration to give N-[4-(3-hydroxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-
35 dihydro-1-benzoxepine-4-carboxamide (Compound 174) (693mg) as pale yellow crystals.

m.p. 285-288°C

¹H-NMR (200MHz, DMSO-d₆) δ 2.34 (3H, s), 2.97 (2H, t, J=4.4 Hz), 4.00 (2H, s), 4.28 (2H, t, J=4.4 Hz), 7.02-7.32 (8H, m), 7.49-7.64 (5H, m), 7.73 (1H, d, J=2.2 Hz), 7.95 (1H, dd, J=4.4, 1.4 Hz), 9.86 (1H, br s).

IR (KBr) 3390, 3028, 1651, 1510, 1408, 1284, 1236, 808 cm⁻¹

Elemental Analysis for C₃₀H₂₆N₂O₃ · 0.2H₂O

Calcd. C, 77.30 ; H, 5.71 ; N, 6.01 ;

Found. C, 77.20 ; H, 5.63 ; N, 5.89.

10 Working Example 175 (Production of Compound 175)

To a suspension of N-[4-(3-hydroxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (400mg) in tetrahydrofuran (30ml) was added 3-chloroperbenzoic acid (70%, 0.32g) at 15 0°C, and the mixture was stirred at room temperature for 15 hours. To the mixture was added sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride 20 solution, dried with magnesium sulfate, concentrated under reduced pressure and recrystallized from ethanol to give N-[4-(1-oxido-3-hydroxypyridin-2-ylmethyl)phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 175) (262mg) as pale yellow crystals.

25 m.p. 254°C (dec.)

¹H-NMR (200MHz, DMSO-d₆) δ 2.34 (3H, s), 2.92-3.02 (2H, m), 4.14 (2H, s), 4.23-4.34 (2H, m), 6.87 (1H, d, J=7.4 Hz), 7.04 (1H, d, J=8.6 Hz), 7.11 (1H, dd, J=8.4, 6.6 Hz), 7.18-7.36 (5H, m), 7.48-7.61 (5H, m), 7.73 (1H, d, J=2.2 30 Hz), 7.83 (1H, dd, J=6.4, 1.0 Hz), 9.88 (1H, s).

IR (KBr) 3180, 3102, 1651, 1601, 1537, 1516, 1493, 1437, 1227, 1036, 816 cm⁻¹

Elemental Analysis for C₃₀H₂₆N₂O₄ · 0.2H₂O

Calcd. C, 74.73 ; H, 5.52 ; N, 5.81 ;

35 Found. C, 74.63 ; H, 5.35 ; N, 5.55.

Working Example 176 (Production of Compound 176)

Under nitrogen atmosphere, oxalyl chloride (0.12ml) was added to a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (250mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and to the solution were added triethylamine (0.25ml) and 1-(4-aminobenzyl)phosphorinane-1-oxide (219.0mg) at 0°C. The mixture was stirred at room temperature for 4 hours, added to vigorously stirred water to stop the reaction and extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from ethanol to give N-(4-(pentamethylene)phosphorylmethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 176) (253mg) as colorless crystals. m.p. 283-286°C

¹H-NMR (200MHz, CDCl₃) δ 1.32-2.09 (10H, m), 2.39 (3H, s), 3.04-3.18 (4H, m), 4.36 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.4 Hz), 7.19-7.29 (5H, m), 7.44-7.48 (3H, m), 7.53 (1H, d, J=2.6 Hz), 7.59 (2H, d, J=8.4 Hz), 8.09 (1H, br s).

IR (KBr) 3217, 2927, 1655, 1599, 1516, 1493, 1321, 1255, 1236, 1167, 1134, 847, 810 cm⁻¹

Elemental Analysis for C₃₀H₃₂NO₃P

Calcd. C, 74.21 ; H, 6.64 ; N, 2.88 ; P, 6.38 ;

Found. C, 73.96 ; H, 6.53 ; N, 3.11 ; P, 6.56.

Working Example 177 (Production of Compound 177)

Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (120mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.12ml) and

- 4-[N-methyl-N-(tetrahydro-pyran-4-yl)aminomethyl]-
aniline (99mg) at 0°C, and the mixture was stirred at room
temperature for 3 hours. The reaction mixture was added to
vigorously stirred water to stop the reaction. The mixture
5 was extracted with ethyl acetate. The organic layer was
washed with saturated sodium chloride solution, dried with
magnesium sulfate and concentrated. The residue was
purified with column chromatography (ethanol/ethyl
acetate=1:5) and recrystallized from ethyl acetate to give
10 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-
phenyl]-7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-
carboxamide (Compound 177) (99mg) as colorless crystals.
m.p. 181-182°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.28 (3H, t, J=7.6 Hz), 1.60-1.82
15 (4H, m), 2.21 (3H, s), 2.57-2.61 (1H, m), 2.69 (2H, q, J=7.6
Hz), 3.09 (2H, t, J=4.6 Hz), 3.37 (2H, dt, J=3.3, 11.1 Hz),
3.58 (2H, s), 3.98-4.09 (2H, m), 4.37 (2H, t, J=4.6 Hz),
7.06 (1H, d, J=8.4 Hz), 7.23-7.36 (5H, m), 7.44-7.58 (7H,
m).
- 20 IR (KBr) 3305, 2960, 1647, 1539, 1514, 1491, 1321, 820 cm⁻¹
Elemental Analysis for C₂₂H₂₆N₂O₃
Calcd. C, 77.39 ; H, 7.31 ; N, 5.64 ;
Found. C, 77.38 ; H, 7.24 ; N, 5.66.
- Working Example 178 (Production of Compound 178)
- 25 Under nitrogen atmosphere, oxalyl chloride (0.06ml)
was added to a solution of 7-(4-ethylphenyl)-2,3-
dihydro-1-benzoxepine-4-carboxylic acid (120mg) in
tetrahydrofuran (10ml) at room temperature. To the mixture
was added a drop of DMF, and the mixture was stirred for
30 1 hour. Under reduced pressure, the solvent was evaporated.
The residue was dissolved in tetrahydrofuran (20ml), and
to the solution were added triethylamine (0.12ml) and
1-(4-aminobenzyl)phosphorinane-1-oxide (100mg) at 0°C, and
the mixture was stirred at room temperature for 5 hours.
- 35 The reaction mixture was added to vigorously stirred water
to stop the reaction, and the mixture was extracted with

chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:5→1:4) and
5 recrystallized from ethanol to give N-(4-(pentamethylene)-phosphorylmethylphenyl)-7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 178) (88mg) as colorless crystals.

m.p. 287-288°C

10 ¹H-NMR (200MHz, CDCl₃) δ 1.28 (3H, t, J=7.4 Hz), 1.42-2.16 (10H, m), 2.70 (2H, q, J=7.4 Hz), 3.05-3.19 (4H, m), 4.37 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.4 Hz), 7.21-7.31 (5H, m), 7.43-7.62 (6H, m), 7.84 (1H, br s).

IR (KBr) 3392, 1655, 1599, 1533, 1516, 1493, 1321, 1255,
15 1167, 847, 824 cm⁻¹

Elemental Analysis for C₃₁H₃₁NO₃P

Calcd. C, 74.53 ; H, 6.86 ; N, 2.80 ; P, 6.20 ;

Found. C, 74.23 ; H, 6.78 ; N, 2.89 ; P, 6.07.

Working Example 179 (Production of Compound 179)

20 Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 7-(4-tert-butylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (130mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for
25 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.12ml) and 4-[N-methyl-N-(tetrahydro-pyran-4-yl)aminomethyl]-aniline (98mg) at 0°C, and the mixture was stirred at room
30 temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was
35 purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate to give

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-tert-butylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 179) (126mg) as colorless crystals.

5 m.p. 193-194°C

¹H-NMR (200MHz, CDCl₃) δ 1.37 (9H, s), 1.60-1.82 (4H, m), 2.21 (3H, s), 2.56-2.75 (1H, m), 3.09 (2H, t, J=4.6 Hz), 3.29-3.45 (2H, m), 3.58 (2H, s), 3.97-4.09 (2H, m), 4.37 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.0 Hz), 7.23-7.35 (3H, m), 7.41-7.58 (9H, m).

10 IR (KBr) 3342, 2949, 1647, 1512, 1406, 1313, 1240, 1136, 822 cm⁻¹

Elemental Analysis for C₃₁H₄₀N₂O₃

Calcd. C, 77.83 ; H, 7.68 ; N, 5.34 ;

15 Found. C, 77.69 ; H, 7.71 ; N, 5.39.

Working Example 180 (Production of Compound 180)

Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 7-(4-tert-butylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (130mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in dichloromethane (10ml), and to the solution were added triethylamine (0.12ml) and 25 1-(4-aminobenzyl)phosphorinane-1-oxide (99mg) at 0°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added to vigorously stirred water to stop the reaction, and the mixture was extracted with dichloromethane. The organic layer was washed with 30 saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give N-(4-(pentamethylene)-phosphorylmethyl-phenyl)-7-(4-tert-butylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 180) 35 (106mg) as colorless crystals.

m.p. 292-294°C

¹H-NMR (200MHz, CDCl₃) δ 1.36 (9H, s), 1.39-2.10 (10H, m), 3.04-3.19 (4H, m), 4.36 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.2 Hz), 7.19-7.30 (3H, m), 7.41-7.63 (8H, m), 8.24 (1H, br s).

5 IR (KBr) 3236, 1664, 1516, 1491, 1311, 1252, 1232, 1163, 1132, 845, 824 cm⁻¹

Elemental Analysis for C₃₃H₃₈NO₃P

Calcd. C, 75.12 ; H, 7.26 ; N, 2.65 ; P, 5.87 ;

Found. C, 74.82 ; H, 7.25 ; N, 2.73 ; P, 5.99.

10 Working Example 181 (Production of Compound 181)

Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (120mg) in tetrahydrofuran (10ml) at room temperature. To the mixture
15 was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.12ml) and
20 4-[N-methyl-N-(tetrahydro-pyran-4-yl)aminomethyl]-aniline (97mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with
25 magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate-diethylether to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 181) (67mg)
30 as colorless crystals.

m.p. 191-192°C

¹H-NMR (200MHz, CDCl₃) δ 1.61-1.83 (4H, m), 2.21 (3H, s), 2.54-2.74 (1H, m), 3.09 (2H, t, J=4.7 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.97-4.09 (2H, m), 4.37 (2H, t, J=4.7 Hz),
35 7.08 (1H, d, J=8.2 Hz), 7.23-7.58 (12H, m).

IR (KBr) 3309, 1643, 1520, 1485, 1319, 1246, 816 cm^{-1}

Elemental Analysis for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_3\text{Cl}$

Calcd. C, 71.63 ; H, 6.21 ; N, 5.57 ; Cl, 7.05 ;

Found. C, 71.32 ; H, 6.21 ; N, 5.60 ; Cl, 6.81.

5 Working Example 182 (Production of Compound 182)

Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (120mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in dichloromethane (10ml). To the solution were added triethylamine (0.12ml) and 1-(4-aminobenzyl)phosphorinane-1-oxide (98mg) at 0°C , and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction, and the mixture was extracted with dichloro-methane. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give N-(4-pentamethylene-phosphorylmethylphenyl)-7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 182) (69mg) as colorless crystals.

m.p. $270-272^\circ\text{C}$

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.31-2.10 (10H, m), 3.04-3.18 (4H, m), 4.37 (2H, t, $J=4.6$ Hz), 7.07 (1H, d, $J=8.4$ Hz), 7.19-7.29 (3H, m), 7.38-7.52 (6H, m), 7.58 (2H, d, $J=8.4$ Hz), 8.07 (1H, br s).

IR (KBr) 3230, 2935, 1655, 1599, 1516, 1483, 1317, 1254, 1230, 1157, 824 cm^{-1}

Elemental Analysis for $\text{C}_{29}\text{H}_{29}\text{NO}_3\text{ClP} \cdot 0.5\text{H}_2\text{O}$

Calcd. C, 67.64 ; H, 5.87 ; N, 2.72 ; Cl, 6.88 ; P, 6.01 ;

Found. C, 67.55 ; H, 5.81 ; N, 2.79 ; Cl, 6.67 ; P, 6.11.

Working Example 183 (Production of Compound 183)

Under nitrogen atmosphere, oxalyl chloride (0.05ml) was added to a solution of 7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (130mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.1ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)amino-methyl]aniline (95mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate-hexane to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 183) (91mg) as colorless crystals.

m.p. 205-209°C

¹H-NMR (200MHz, CDCl₃) δ 1.69-1.82 (4H, m), 2.21 (3H, s), 2.55-2.74 (1H, m), 3.10 (2H, t, J=4.7 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.99-4.11 (2H, m), 4.39 (2H, t, J=4.7 Hz), 7.11 (1H, d, J=8.4 Hz), 7.25-7.34 (3H, m), 7.46-7.58 (5H, m), 7.62-7.71 (4H, m).

IR (KBr) 3315, 2958, 2846, 1643, 1522, 1327, 1165, 1115, 1072, 835, 822 cm⁻¹

Elemental Analysis for C₃₁H₃₁N₂O₃F₃

Calcd. C, 69.39 ; H, 5.82 ; N, 5.22 ; F, 10.62 ;

Found. C, 69.21 ; H, 5.79 ; N, 5.24 ; F, 10.60.

Working Example 184 (Production of Compound 184)

Under nitrogen atmosphere, oxalyl chloride (0.05ml) was added to a solution of 7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (130mg) in

- tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml).
- 5 To the solution were added triethylamine (0.1ml) and 1-(4-aminobenzyl)phosphorinane-1-oxide (94.5mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl
- 10 acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate-hexane to give N-(4-
- 15 (pentamethylene)phosphorylmethyl-phenyl)-7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 184) (111mg) as colorless crystals. m.p. 269°C (dec.)
- ¹H-NMR (200MHz, CDCl₃) δ 1.19-2.08 (10H, m), 3.03-3.16 (4H, m), 4.38 (2H, t, J=4.6 Hz), 7.10 (1H, d, J=8.4 Hz), 7.15-7.30 (3H, m), 7.48 (1H, dd, J=8.4, 2.2 Hz), 7.52-7.73 (7H, m), 8.39-8.46 (1H, m).
- 20 IR (KBr) 3221, 2937, 1657, 1533, 1516, 1327, 1257, 1167, 1128, 1072, 849, 825 cm⁻¹
- 25 Elemental Analysis for C₃₀H₂₉NO₃F₃P · 0.2H₂O
Calcd. C, 66.34 ; H, 5.46 ; N, 2.58 ;
Found. C, 66.21 ; H, 5.62 ; N, 2.61.
- Working Example 185 (Production of Compound 185)
- Under nitrogen atmosphere, oxalyl chloride (0.08ml)
- 30 was added to a solution of 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (154.8mg) in tetrahydro-furan (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was
- 35 evaporated. The residue was dissolved in tetrahydrofuran (20ml), and to the solution were added triethylamine (0.2ml)

and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-
aniline (121mg) at 0°C, and the mixture was stirred at room
temperature for 3 hours. The reaction mixture was added to
vigorously stirred water to stop the reaction. The mixture
5 was extracted with ethyl acetate. The organic layer was
washed with saturated sodium chloride solution, dried with
magnesium sulfate and concentrated. The residue was
purified with column chromatography (ethanol/ethyl
acetate=1:4) and recrystallized from ethanol to give 7-
10 (4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-
yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-
carboxamide (Compound 185) (202mg) as colorless crystals.
m.p. 174-176°C

¹H-NMR (200MHz, CDCl₃) δ 1.44 (3H, t, J=7.0 Hz), 1.62-1.82
15 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.08 (2H, t, J=4.8
Hz), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.97-4.10 (2H, m),
4.08 (2H, q, J=7.0 Hz), 4.36 (2H, t, J=4.8 Hz), 6.96 (2H,
d, J=8.8 Hz), 7.05 (1H, d, J=8.4 Hz), 7.24-7.58 (10H, m).
IR (KBr) 3327, 2947, 1645, 1608, 1514, 1495, 1240, 1180,
20 1051, 822 cm⁻¹

Elemental Analysis for C₃₂H₃₆N₂O₄

Calcd. C, 74.97 ; H, 7.08 ; N, 5.46 ;

Found. C, 74.88 ; H, 7.27 ; N, 5.50.

Working Example 186 (Production of Compound 186)

25 Under nitrogen atmosphere, oxalyl chloride (0.06ml)
was added to a solution of 7-(4-trifluoromethoxyphenyl)-
2,3-dihydro-1-benzoxepine-4-carboxylic acid (150mg) in
tetrahydrofuran (10ml) at room temperature. To the mixture
was added a drop of DMF, and the mixture was stirred for
30 1 hour. Under reduced pressure, the solvent was evaporated,
and the residue was dissolved in tetrahydrofuran (10ml).
To the solution were added triethylamine (0.12ml) and
4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline
(104mg) at 0°C, and the mixture was stirred at room
35 temperature for 3 hours. The reaction mixture was added to
vigorously stirred water to stop the reaction. The mixture

- was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:4), and recrystallized from ethyl acetate-hexane to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-trifluoromethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 186) (143mg) as colorless crystals.
- 5 m.p. 187-188°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.62-1.82 (4H, m), 2.21 (3H, s), 2.55-2.74 (1H, m), 3.10 (2H, t, J=4.7 Hz), 3.29-3.45 (2H, m), 3.57 (2H, s), 3.99-4.10 (2H, m), 4.38 (2H, t, J=4.7 Hz), 7.09 (1H, d, J=8.4 Hz), 7.22-7.35 (3H, m), 7.40-7.60 (9H, m).
- 15 IR (KBr) 3319, 2960, 2845, 1643, 1520, 1493, 1319, 1261, 1205, 1163, 835, 810 cm⁻¹
- Elemental Analysis for C₃₁H₃₁N₂O₄F₃
- Calcd. C, 67.38 ; H, 5.65 ; N, 5.07 ; F, 10.31 ;
- 20 Found. C, 67.39 ; H, 5.38 ; N, 5.07 ; F, 10.18.
- Working Example 187 (Production of Compound 187)
- Under nitrogen atmosphere, oxalyl chloride (0.07ml) was added to a solution of (E)-3-(4-methylphenyl)cinnamic acid (125mg) in tetrahydrofuran (10ml) at room temperature.
- 25 To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.14ml) and (4-aminobenzyl)diethylphosphine oxide (120mg) in tetrahydrofuran (5ml) at 0°C, and the mixture was
- 30 stirred at room temperature for 1.5 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate.
- The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and
- 35 recrystallized from ethanol-ethyl acetate to give (E)-

N-(4-diethylphosphorylmethylphenyl)-3-(4-methylphenyl)-
cinnamamide (Compound 187) (125mg) as pale yellow crystals.
m.p. 197-198°C

¹H-NMR (200MHz, CDCl₃) δ 1.13 (6H, dt, J=16.6, 8.0 Hz),
5 1.55-1.71 (4H, m), 2.41 (3H, m), 3.08 (2H, d, J=13.2 Hz),
6.81 (1H, d, J=15.4 Hz), 7.15-7.30 (4H, m), 7.41-7.62 (7H,
m), 7.74-7.84 (2H, m), 8.93-9.02 (1H, m).

IR (KBr) 3242, 1678, 1630, 1603, 1541, 1514, 1409, 1344,
1250, 1165, 1130, 985, 847, 791 cm⁻¹

10 Elemental Analysis for C₂₇H₃₀NO₂P · 0.3H₂O

Calcd. C, 74.22 ; H, 7.06 ; N, 3.21 ; P, 7.09 ;

Found. C, 73.96 ; H, 6.77 ; N, 3.34 ; P, 7.01.

Working Example 188 (Production of Compound 188)

Under nitrogen atmosphere, oxalyl chloride (0.27ml)
15 was added to a solution of (E)-3-(4-methylphenyl)cinnamic
acid (0.50g) in tetrahydrofuran (10ml) at room temperature.
To the mixture was added a drop of DMF, and the mixture was
stirred for 1 hour. Under reduced pressure, the solvent was
evaporated, and the residue was dissolved in tetra-
20 hydrofuran (10ml). To the solution were added triethyl-
amine (0.60ml) and 2-(4-aminophenyl)pyridine (0.39g), and
the mixture was stirred at room temperature for 2 hours.

The reaction mixture was added to vigorously stirred water
to stop the reaction. The mixture was extracted with ethyl
25 acetate. The organic layer was washed with saturated sodium
chloride solution, dried with magnesium sulfate,
concentrated under reduced pressure and recrystallized from
tetrahydrofuran-hexane (1:1) to give (E)-N-[4-(2-
pyridyl)phenyl]-3-(4-methylphenyl)cinnamamide (Compound
30 188) (561mg) as pale yellow crystals.
m.p. 220-222°C

¹H-NMR (200MHz, CDCl₃) δ 2.42 (3H, s), 6.63 (1H, d, J=15.4
Hz), 7.18-7.31 (3H, m), 7.44-7.63 (6H, m), 7.70-7.83 (5H,
m), 7.85 (1H, d, J=15.4 Hz), 8.02 (2H, d, J=8.8 Hz), 8.66-8.72
35 (1H, m).

IR (KBr) 3286, 1657, 1622, 1597, 1524, 1462, 1333, 1180,

970, 787 cm^{-1}

Elemental Analysis for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O} \cdot 0.1\text{H}_2\text{O}$

Calcd. C, 82.67 ; H, 5.70 ; N, 7.14 ;

Found. C, 82.45 ; H, 5.70 ; N, 7.13.

5 Working Example 189 (Production of Compound 189)

To a solution of (E)-N-[4-(2-pyridyl)phenyl]-3-(4-methylphenyl)cinnamamide (350mg) in tetrahydrofuran (10ml) and dichloromethane (30ml) was added 3-chloro-perbenzoic acid (70%, 0.27g) at 0°C , and the mixture was stirred at room temperature for 2 days. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes and extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:1) concentrated to give crystals, which were recrystallized from ethanol-chloroform to give (E)-N-[4-(1-oxidopyridin-2-yl)phenyl]-3-(4-methylphenyl)cinnamamide (Compound 189) (188mg) as pale yellow crystals.

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15
20

m.p. $240-241^\circ\text{C}$

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 2.43 (3H, s), 6.63 (1H, d, $J=15.4$ Hz), 6.98-7.07 (1H, m), 7.24-7.35 (4H, m), 7.37-7.68 (10H, m), 7.78 (1H, d, $J=15.4$ Hz), 8.33-8.36 (1H, m), 8.58-8.66 (1H, m).

25

IR (KBr) 3300, 1680, 1630, 1595, 1529, 1475, 1342, 1225, 970, 837, 766 cm^{-1}

Elemental Analysis for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_2$

Calcd. C, 79.78 ; H, 5.46 ; N, 6.89 ;

30 Found. C, 79.71 ; H, 5.39 ; N, 6.93.

Working Example 190 (Production of Compound 190)

Under nitrogen atmosphere, oxalyl chloride (0.22ml) was added to a solution of (E)-3-(4-methylphenyl)cinnamic acid (0.40g) in tetrahydrofuran (10ml) at room temperature.

35

To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was

evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.50ml) and 2-(4-amino-benzyl)pyridine (0.34g) in tetrahydrofuran (5ml) at 0°C, and the mixture was stirred at room temperature
5 for 2 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate, concentrated and recrystallized from
10 ethyl acetate-hexane to give (E)-N-[4-(2-pyridylmethyl)-phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 190) (490mg) as yellow crystals.

m.p. 169-171°C

¹H-NMR (200MHz, CDCl₃) δ 2.41 (3H, s), 4.14 (2H, s), 6.60
15 (1H, d, J=15.4 Hz), 7.10-7.15 (2H, m), 7.22-7.28 (4H, m), 7.42-7.63 (9H, m), 7.71 (1H, br s), 7.80 (1H, d, J=15.4 Hz), 8.53-8.58 (1H, m).

IR (KBr) 3238, 1673, 1630, 1601, 1539, 1512, 1348, 1248, 1174, 976, 791, 760 cm⁻¹

20 Elemental Analysis for C₂₈H₂₄N₂O · 0.1H₂O

Calcd. C, 82.77 ; H, 6.00 ; N, 6.89 ;

Found. C, 82.73 ; H, 5.89 ; N, 6.97.

Working Example 191 (Production of Compound 191)

To a solution of (E)-N-[4-(2-pyridylmethyl)phenyl]-
25 3-(4-methylphenyl)cinnamamide (302mg) in tetrahydrofuran (10ml) was added 3-chloroperbenzoic acid (70%, 0.27g) at 0°C, and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes.
30 The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was recrystallized from ethanol to give (E)-N-[4-(1-oxidopyridin-2-ylmethyl)-
35 phenyl]-3-(4-methylphenyl)cinnamamide (Compound 191) (180mg) as pale yellow crystals.

m.p. 183-185°C

¹H-NMR (200MHz, CDCl₃) δ 2.41 (3H, s), 4.24 (2H, s), 6.64 (1H, d, J=15.4 Hz), 6.96-7.01 (1H, m), 7.12-7.17 (2H, m), 7.22-7.30 (4H, m), 7.40-7.51 (4H, m), 7.54-7.63 (3H, m), 7.66-7.74 (2H, m), 7.82 (1H, d, J=15.4 Hz), 8.29-8.31 (1H, m).

IR (KBr) 3255, 1684, 1605, 1541, 1514, 1412, 1346, 1244, 839, 785 cm⁻¹

Elemental Analysis for C₂₁H₂₄N₂O₂

Calcd. C, 79.98 ; H, 5.75 ; N, 6.66 :

Found. C, 80.18 ; H, 5.63 ; N, 6.69.

Working Example 192 (Production of Compound 192)

Under nitrogen atmosphere, oxalyl chloride (0.27ml) was added to a solution of (E)-3-(4-methylphenyl)cinnamic acid (0.50g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.60ml) and 3-(4-aminophenyl)pyridine (0.39g) at 0°C, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethyl acetate) to give yellow crystals, which were recrystallized from tetrahydrofuran-ethanol to give (E)-N-[4-(3-pyridyl)phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 192) (447mg) as pale yellow crystals.

m.p. 213-214°C

¹H-NMR (200MHz, CDCl₃) δ 2.15 (3H, s), 6.65 (1H, d, J=15.4 Hz), 7.26-7.64 (11H, m), 7.75-7.90 (5H, m), 8.59 (1H, dd, J=4.8, 1.8 Hz), 8.85 (1H, d, J=1.8 Hz).

IR (KBr) 3344, 1660, 1626, 1525, 1481, 1335, 1171, 978, 795 cm⁻¹

Elemental Analysis for $C_{27}H_{22}N_2O$

Calcd. C, 83.05 ; H, 5.68 ; N, 7.17 :

Found. C, 83.01 ; H, 5.82 ; N, 7.23.

Working Example 193 (Production of Compound 193)

- 5 To a solution of (E)-N-[4-(3-pyridyl)phenyl]-3-(4-methylphenyl)cinnamamide (250mg) in tetrahydrofuran (20ml) was added 3-chloroperbenzoic acid (70%, 0.24g) at 0°C, and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added sodium thiosulfate
10 solution, and the mixture was stirred for a few minutes and extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was recrystallized
15 from ethanol-tetrahydrofuran-acetone to give (E)-N-[4-(1-oxidopyridin-3-yl)phenyl]-3-(4-methylphenyl)-cinnamamide (Compound 193) (208mg) as pale yellow crystals.
 $^1\text{H-NMR}$ (200MHz, DMSO- d_6) δ 2.38 (3H, s), 6.95 (1H, d, J=15.7 Hz), 7.31 (2H, d, J=8.1 Hz), 7.45-7.57 (2H, m), 7.59-7.94
20 (12H, m), 8.19 (1H, d, J=6.5 Hz), 8.58 (1H, s).
IR (KBr) 3423, 1672, 1597, 1531, 1477, 1340, 1201, 901, 835, 793 cm^{-1}

Working Example 194 (Production of Compound 194)

- 25 Under nitrogen atmosphere, oxalyl chloride (0.19ml) was added to a solution of (E)-3-(4-methylphenyl)cinnamic acid (340mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran
30 (10ml). To the solution were added triethylamine (0.4ml) and 4-aminobenzyl-dipropylphosphine oxide (0.38g) at 0°C, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl
35 acetate. The organic layer was concentrated. The residue was recrystallized from ethanol to give (E)-N-(4-dipropyl-

phosphorylmethyl-phenyl)-3-(4-methylphenyl)cinnamamide
(Compound 194) (489mg) as colorless crystals.

m.p. 225-227°C

¹H-NMR (200MHz, DMSO-d₆) δ 0.87-1.00 (6H, m), 1.37-1.63 (8H, m), 2.37 (3H, s), 3.07 (2H, d, J=15.0 Hz), 6.93 (1H, d, J=16.0 Hz), 7.16-7.25 (2H, m), 7.30 (2H, d, J=8.0 Hz), 7.50-7.71 (9H, m), 7.89 (1H, br s).

IR (KBr) 3232, 1676, 1624, 1605, 1545, 1512, 1338, 1151 cm⁻¹

Elemental Analysis for C₂₃H₂₁NO₂P

10 Calcd. C, 75.79 ; H, 7.46 ; N, 3.05 ; P, 6.74 ;

Found. C, 75.60 ; H, 7.68 ; N, 2.99 ; P, 6.83.

Working Example 195 (Production of Compound 195)

Under nitrogen atmosphere, oxalyl chloride (0.11ml) was added to a solution of (E)-3-(4-methylphenyl)cinnamic acid (200mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.25ml) and 1-(4-aminobenzyl)phosphorane-1-oxide (193mg) at 0°C, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and concentrated. The residue was recrystallized from ethanol to give (E)-N-(4-(tetramethylene)phosphoryl-methylphenyl)-3-(4-methylphenyl)-cinnamamide (Compound 195) (221mg) as colorless crystals. m.p. 273-275°C

30 ¹H-NMR (200MHz, CDCl₃) δ 1.48-2.04 (8H, m), 2.41 (3H, s), 3.19 (2H, d, J=13.6 Hz), 6.78 (1H, d, J=15.8 Hz), 7.14-7.31 (4H, m), 7.43-7.59 (7H, m), 7.73-7.76 (1H, m), 7.79 (1H, d, J=15.8 Hz), 8.75-8.84 (1H, m).

IR (KBr) 3232, 1676, 1628, 1603, 1543, 1512, 1410, 1341, 35 1171, 985, 868, 793 cm⁻¹

Elemental Analysis for C₂₇H₂₈NO₂P · 0.3H₂O

Calcd. C, 74.56 ; H, 6.62 ; N, 3.22 ; P, 7.12 ;

Found. C, 74.36 ; H, 6.64 ; N, 3.20 ; P, 7.06.

Working Example 196 (Production of Compound 196)

Under nitrogen atmosphere, oxalyl chloride (0.12ml)
5 was added to a solution of (E)-3-(4-methylphenyl)cinnamic
acid (220mg) in tetrahydrofuran (10ml) at room temperature.
To the mixture was added a drop of DMF, and the mixture was
stirred for 1 hour. Under reduced pressure, the solvent was
evaporated. The residue was dissolved in tetrahydrofuran
10 (20ml), and to the solution were added triethylamine
(0.26ml) and 1-(4-amino-benzyl)phosphorinane-1-oxide
(226mg) at 0°C. The mixture was stirred at room temperature
for 20 hours. The reaction mixture was added to vigorously
stirred water to stop the reaction, and the mixture was
15 extracted with chloroform. The organic layer was washed
with saturated sodium chloride solution, dried with
magnesium sulfate and concentrated. The residue was
recrystallized from ethanol to give (E)-N-(4-(penta-
methylene)phosphorylmethylphenyl)-3-(4-methylphenyl)-
20 cinnamamide (Compound 196) (271mg) as colorless crystals.
m.p. 273-276°C

¹H-NMR (200MHz, CDCl₃) δ 1.43-2.08 (10H, m), 2.41 (3H, s),
3.13 (2H, d, J=12.8 Hz), 6.81 (1H, d, J=15.8 Hz), 7.14-
7.30 (4H, m), 7.41-7.61 (7H, m), 7.76 (1H, s), 7.80 (1H,
25 d, J=15.8 Hz), 8.72-8.87 (1H, m).

IR (KBr) 3242, 1676, 1628, 1603, 1539, 1514, 1344, 1174,
1155, 1126, 991, 789 cm⁻¹

Elemental Analysis for C₂₈H₃₀NO₂P · 1.5H₂O

Calcd. C, 71.47 ; H, 7.06 ; N, 2.98 ; P, 6.58 ;

30 Found. C, 71.53 ; H, 6.99 ; N, 2.87 ; P, 6.76.

Working Example 197 (Production of Compound 197)

Under nitrogen atmosphere, oxalyl chloride (0.20ml)
was added to a solution of 6-(4-methylphenyl)-2H-1-benzo-
pyran-3-carboxylic acid (300mg) in tetrahydrofuran (10ml)
35 at room temperature. To the mixture was added a drop of DMF,
and the mixture was stirred for 1 hour. Under reduced

pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.31ml) and 1-(4-aminobenzyl)-piperidine (0.24g) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:5) to give N-[4-(1-piperidinylmethyl)phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 197) (324mg) as yellow crystals.

m.p. 196-197°C

¹H-NMR (200MHz, CDCl₃) δ 1.41-1.71 (6H, m), 2.34-2.43 (7H, m), 3.46 (2H, s), 5.12 (2H, d, J=1.4 Hz), 6.95 (1H, d, J=8.0 Hz), 7.14 (1H, br s), 7.23-7.29 (3H, m), 7.31-7.38 (2H, m), 7.40-7.46 (6H, m).

IR (KBr) 3361, 1643, 1601, 1529, 1485, 1317, 1254, 810 cm⁻¹

Elemental Analysis for C₂₈H₃₀N₂O₂ · 0.1H₂O

Calcd. C, 79.10 ; H, 6.91 ; N, 6.36 :

Found. C, 78.85 ; H, 6.90 ; N, 6.26.

Working Example 198 (Production of Compound 198)

To a solution of N-[4-(1-piperidinylmethyl)phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (200mg) in DMF (3ml) was added methyl iodide (0.1ml) at room temperature, and the mixture was stirred for 20 hours. To the mixture was added ethyl acetate. Precipitated crystal was collected by filtration and recrystallized from chloroform-ethanol to give 1-[4-[N-[6-(4-methylphenyl)-2H-1-benzopyran-3-carbonyl]-amino]benzyl]-1-methylpiperidinium iodide (Compound 198) (188mg) as yellow crystals.

m.p. 210°C (dec.)

¹H-NMR (200MHz, CDCl₃) δ 1.62-2.01 (6H, m), 2.36 (3H, s), 3.06 (3H, br s), 3.34-3.49 (2H, m), 3.60-3.76 (2H, m), 4.97 (2H, br s), 5.04 (2H, br s), 6.85 (1H, d, J=8.4 Hz), 7.17

(2H, d, $J=8.2$ Hz), 7.37-7.42 (3H, m), 7.47-7.52 (3H, m), 7.83-7.91 (3H, m), 9.00 (1H, br s).

IR (KBr) 3246, 1668, 1527, 1483, 1319, 1248, 808 cm^{-1}

Elemental Analysis for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_2\text{I} \cdot 0.2\text{H}_2\text{O}$

5 Calcd. C, 61.69 ; H, 5.76 ; N, 4.80 ;

Found. C, 61.53 ; H, 5.72 ; N, 4.85.

Working Example 199 (Production of Compound 199)

Under nitrogen atmosphere, oxalyl chloride (0.26ml) was added to a solution of 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (0.52g) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in tetrahydrofuran (6ml), and to the solution were added triethylamine (0.60ml) and 2-(4-aminobenzyl)-pyridine (0.40g) in tetrahydrofuran (5ml), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=2:1) and concentrated to give crystals, which were recrystallized from ethanol-ethyl acetate) to give N-[4-(2-pyridylmethyl)phenyl]-6-(4-methyl-phenyl)-2H-1-benzopyran-3-carboxamide (Compound 199) (353.2mg) as yellow crystals, which were similarly recrystallized to give the second crystals (208mg).

30 m.p. 184-187°C

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 2.39 (3H, m), 4.14 (2H, s), 5.10 (2H, d, $J=1.4$ Hz), 6.93 (1H, d, $J=8.4$ Hz), 7.09-7.15 (3H, m), 7.19-7.32 (5H, m), 7.37-7.66 (7H, m), 8.53-8.57 (1H, m).

35 IR (KBr) 3296, 1639, 1599, 1531, 1514, 1473, 1325, 1259 cm^{-1}
Elemental Analysis for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$

Calcd. C, 80.53 ; H, 5.59 ; N, 6.48 :

Found. C, 80.24 ; H, 5.75 ; N, 6.43.

Working Example 200 (Production of Compound 200)

To a solution of N-[4-(2-pyridylmethyl)phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (250mg) in tetrahydrofuran (10ml) was added 3-chloroperbenzoic acid (70%, 0.21g) at 0°C, and the mixture was stirred at room temperature for 14 hours. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:3) concentrated to give crystals, which were recrystallized from chloroform-ethanol to give N-[4-(1-oxidopyridin-2-ylmethyl)phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 200) (191mg) as pale yellow crystals.

m.p. 261-263°C

¹H-NMR (200MHz, CDCl₃) δ 2.40 (3H, s), 4.25 (2H, s), 5.11 (2H, s), 6.92-7.01 (2H, m), 7.13-7.67 (14H, m), 8.29 (1H, t, J=4.2 Hz).

IR (KBr) 3302, 1660, 1605, 1537, 1520, 1250 cm⁻¹

Elemental Analysis for C₂₄H₂₄N₂O₃

Calcd. C, 77.66 ; H, 5.39 ; N, 6.25 :

Found. C, 77.90 ; H, 5.37 ; N, 6.21.

Working Example 201 (Production of Compound 201)

Under nitrogen atmosphere, oxalyl chloride (0.19ml) was added to a solution of 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (380mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.4ml) and 4-aminobenzylidipropyl-

phosphine oxide (0.38g) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was concentrated, and the residue was recrystallized from ethanol to give N-(4-dipropylphosphoryl-methyl-phenyl)-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 201) (460mg) as pale yellow crystals. m.p. 192-194°C

¹H-NMR (200MHz, CDCl₃) δ 0.83-0.97 (6H, m), 1.39-1.68 (8H, m), 2.39 (3H, s), 3.05 (2H, d, J=13.2 Hz), 5.12 (2H, d, J=0.8 Hz), 6.94 (1H, d, J=8.4 Hz), 7.11-7.28 (4H, m), 7.31-7.50 (5H, m), 7.61 (2H, d, J=8.4 Hz), 9.13-9.24 (1H, m). IR (KBr) 3265, 1664, 1628, 1603, 1539, 1514, 1487, 1325, 1252, 1167, 851 cm⁻¹

Elemental Analysis for C₃₀H₃₄NO₃P

Calcd. C, 73.90 ; H, 7.03 ; N, 2.87 ; P, 6.35 ;

Found. C, 73.95 ; H, 6.87 ; N, 2.84 ; P, 6.41.

Working Example 202 (Production of Compound 202)

Under nitrogen atmosphere, oxalyl chloride (0.19ml) was added to a solution of 6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxylic acid (400mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.4ml) and (4-amino-phenyl)-(2-pyridyl)methanol (310mg) at 0°C, and the mixture was stirred at room temperature for 20 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. Precipitated crystal was recrystallized from tetrahydrofuran-hexane to give N-[4-[hydroxy(2-pyridyl)methyl]-phenyl]-6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxamide

(Compound 202) (470mg) as yellow crystals.

m.p. 202-205°C

¹H-NMR (200MHz, CDCl₃) δ 1.47 (3H, d, J=6.6 Hz), 2.39 (3H, s), 5.29-5.38 (1H, m), 5.48 (1H, q, J=6.6 Hz), 5.74 (1H, br s), 6.94 (1H, d, J=8.0 Hz), 7.08-7.26 (5H, m), 7.33-7.67 (10H, m), 8.57 (1H, d, J=4.6 Hz).

IR (KBr) 3255, 1647, 1597, 1518, 1485, 1412, 1317, 1255, 812, 756 cm⁻¹

Elemental Analysis for C₃₀H₂₆N₂O₃ · 0.2H₂O

10 Calcd. C, 77.30 ; H, 5.70 ; N, 6.01 ;

Found. C, 77.31 ; H, 5.60 ; N, 6.21.

Working Example 203 (Production of Compound 203)

To a solution of N-[4-[hydroxy(2-pyridyl)methyl]-phenyl]-6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxamide (300mg) in tetrahydrofuran (10ml) was added 3-chloroperbenzoic acid (70%, 0.24g) at 0°C, and the mixture was stirred at room temperature for 24 hours. To the mixture was added sodium thiosulfate, and the mixture was stirred for a few minutes. was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:2) to give crystals, which were recrystallized from ethanol-ethyl acetate to give N-[4-[hydroxy(1-oxidopyridin-2-yl)-methyl]phenyl]-6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxamide (Compound 203) (129mg) as pale yellow crystals.

m.p. 230-232°C

30 ¹H-NMR (200MHz, CDCl₃) δ 1.49 (3H, d, J=6.6 Hz), 2.40 (3H, s), 5.50 (1H, q, J=6.6 Hz), 6.07 (1H, d, J=4.5 Hz), 6.40 (1H, d, J=4.5 Hz), 6.93-6.97 (2H, m), 7.12 (1H, s), 7.22-7.29 (4H, m), 7.35 (1H, d, J=2.2 Hz), 7.42-7.50 (5H, m), 7.64 (2H, d, J=8.4 Hz), 7.73 (1H, br s), 8.24-8.28 (1H, m).

35 IR (KBr) 3311, 1664, 1603, 1535, 1485, 1321, 1252, 812 cm⁻¹

Elemental Analysis for C₃₀H₂₆N₂O₄ · 0.3H₂O

Calcd. C, 74.46 ; H, 5.54 ; N, 5.79 :

Found. C, 74.41 ; H, 5.46 ; N, 5.78.

Working Example 204 (Production of Compound 204)

Under nitrogen atmosphere, oxalyl chloride (0.11ml)
5 was added to a solution of 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (230mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was
10 dissolved in tetrahydrofuran (20ml), and to the solution were added triethylamine (0.25ml) and 1-(4-aminobenzyl)-phosphorane-1-oxide (200mg) at 0°C, and the mixture was stirred at room temperature for 20 hours. The reaction mixture was added to vigorously stirred water to stop the
15 reaction. Precipitated crystal was collected by filtration to give N-(4-tetramethylenephosphorylmethyl-phenyl)-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 204) (181mg) as colorless crystals.

m.p. >300°C

20 ¹H-NMR (200MHz, CDCl₃) δ 1.49-2.04 (8H, m), 2.40 (3H, s), 3.22 (2H, d, J=14.4 Hz), 5.12 (2H, s), 6.94 (1H, d, J=8.4 Hz), 7.21-7.29 (4H, m), 7.34-7.50 (5H, m), 7.58 (2H, d, J=8.4 Hz), 8.04-8.07 (1H, m).

IR (KBr) 3236, 1657, 1601, 1535, 1518, 1487, 1323, 1255,
25 1180, 810 cm⁻¹.

Elemental Analysis for C₂₈H₂₈NO₃P · 0.3H₂O

Calcd. C, 72.65 ; H, 6.23 ; N, 3.03 ; P, 6.69 :

Found. C, 72.30 ; H, 5.90 ; N, 3.00 ; P, 6.98.

Working Example 205 (Production of Compound 205)

30 Under nitrogen atmosphere, oxalyl chloride (0.12ml) was added to a solution of 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (240mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced
35 pressure, the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and to the solution

were added triethylamine (0.25ml) and 1-(4-aminobenzyl)-phosphorinane-1-oxide (221mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction.

5 The mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give N-(4-(pentamethylene)phosphorylmethylphenyl)-6-(4-

10 methylphenyl)-2H-1-benzo-pyran-3-carboxamide (Compound 205) (257mg) as yellow crystals.

m.p. 268°C (dec.)

¹H-NMR (200MHz, CDCl₃) δ 1.39-2.15 (10H, m), 2.40 (3H, s), 3.14 (2H, d, J=12.8 Hz), 5.12 (2H, s), 6.94 (1H, d, J=8.0

15 Hz), 7.18-7.49 (9H, m), 7.59 (2H, d, J=8.4 Hz), 8.54 (1H, br s).

IR (KBr) 3296, 1660, 1533, 1514, 1323, 1255, 1163, 845, 812 cm⁻¹

Elemental Analysis for C₂₂H₂₀NO₃P

20 Calcd. C, 73.87 ; H, 6.41 ; N, 2.97 ; P, 6.57 :

Found. C, 74.20 ; H, 6.39 ; N, 2.78 ; P, 6.45.

Working Example 206 (Production of Compound 206)

Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 6-(4-methylphenyl)-2H-1-benzo-

25 pyran-3-carboxylic acid (120mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in tetra-hydrofuran (20ml). To the solution were

30 added triethylamine (0.2ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-aniline (109mg) at 0°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl

35 acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and

concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:4), and recrystallized from ethyl acetate-hexane to give N-[4-[N-methyl-N-(tetrahydro-
5 pyran-4-yl)aminomethyl]-phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 206) (117mg) as pale yellow crystals.

m.p. 143-145°C

¹H-NMR (200MHz, CDCl₃) δ 1.62-1.84 (4H, m), 2.21 (3H, s),
10 2.40 (3H, s), 2.56-2.74 (1H, m), 3.28-3.45 (2H, m), 3.57 (2H, s), 3.98-4.11 (2H, m), 5.12 (2H, d, J=1.0 Hz), 6.94 (1H, d, J=8.4 Hz), 7.15 (1H, br s), 7.21-7.37 (5H, m), 7.39-7.59 (6H, m).

IR (KBr) 3280, 2937, 2848, 1649, 1597, 1539, 1489, 1336,
15 1257, 1138, 1007, 810 cm⁻¹

Elemental Analysis for C₃₀H₃₂N₂O₃

Calcd. C, 76.90 ; H, 6.88 ; N, 5.98 :

Found. C, 76.56 ; H, 6.87 ; N, 6.00.

Working Example 207 (Production of Compound 207)

20 Under nitrogen atmosphere, oxalyl chloride (0.06ml) was added to a solution of 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (120m) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced
25 pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml). To the solution were added triethylamine (0.13ml) and 4-[N-methyl-N-(tetrahydrothiopyran-4-yl)amino-methyl]aniline (117mg) at 0°C, and the mixture was stirred at room temperature for 4 hours.
30 The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was
35 separated and purified with column chromatography (ethanol/ethyl acetate=1:4), and recrystallized from ethyl

acetate-hexane to give N-[4-[N-methyl-N-(tetrahydrothiopyran-4-yl)aminomethyl]phenyl]-6-(4-methylphenyl)-2H-1-benzopyran-3-carboxamide (Compound 207) (125mg) as pale yellow crystals.

5 m.p. 169-171°C

¹H-NMR (200MHz, CDCl₃) δ 1.63-1.80 (2H, m), 2.09-2.24 (2H, m), 2.21 (3H, s), 2.40 (3H, s), 2.42-2.56 (1H, m), 2.64-2.74 (4H, m), 3.57 (2H, s), 5.12 (2H, d, J=1.0 Hz), 6.94 (1H, d, J=8.8 Hz), 7.15 (1H, br s), 7.23-7.36 (5H, m), 7.39-7.57 (6H, m).

10 IR (KBr) 3286, 2922, 1649, 1597, 1539, 1336, 1319, 1261, 808 cm⁻¹

C₃₀H₃₁N₂O₂S

Calcd. C, 74.35 ; H, 6.65 ; N, 5.78 ; S, 6.62 ;

15 Found. C, 74.25 ; H, 6.47 ; N, 5.91 ; S, 6.52.

Working Example 208 (Production of Compound 208)

To a solution of (E)-3-[5-(4-methylphenyl)thiophen-2-yl]acrylic acid (400mg) in tetrahydrofuran (10ml) was added oxalyl chloride (0.22ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml). To the solution were added triethylamine (0.46ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (0.40g) at 0°C, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give (E)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-3-[5-(4-methylphenyl)thiophen-2-yl]acrylic amide (Compound 208) (293mg) as yellow crystal.

35 m.p. 199-201°C

¹H-NMR (200MHz, CD₃OD) δ 1.57-1.95 (4H, m), 2.32 (3H, s),

2.36 (3H, s), 2.74-2.96 (1H, m), 3.32-3.47 (2H, m), 3.76 (2H, s), 3.96-4.09 (2H, m), 6.55 (1H, d, J=15.2 Hz), 7.23 (2H, d, J=8.4 Hz), 7.29-7.36 (4H, m), 7.56 (2H, d, J=8.0 Hz), 7.66 (2H, d, J=8.4 Hz), 7.75 (1H, d, J=15.2Hz).

5 IR (KBr) 3359, 1668, 1608, 1554, 1512, 1363, 802 cm^{-1}

Elemental Analysis for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_2\text{S} \cdot 1.2\text{H}_2\text{O}$

Calcd. C, 69.26 ; H, 6.97 ; N, 5.98 :

Found. C, 69.28 ; H, 6.90 ; N, 6.06.

Working Example 209 (Production of Compound 209)

10 To a solution of (E)-3-[5-(4-methylphenyl)thiophen-2-yl]acrylic acid (150mg) in tetrahydrofuran (10ml) was added oxalyl chloride (0.1ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was
15 evaporated, and the residue was dissolved in tetrahydrofuran (30ml). To the solution were added triethylamine (0.2ml) and 1-(4-aminobenzyl)phosphorinane-1-oxide (150mg) at 0°C, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was added to vigorously stirred water
20 to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give (E)-N-(4-penta-
25 methylenephosphorylmethylphenyl)-3-[5-(4-methylphenyl)-thiophen-2-yl]acrylic amide (Compound 209) (172mg) as yellow crystals.

m.p. 294-297°C

¹H-NMR (200MHz, CDCl_3) δ 1.35-2.13 (10H, m), 2.29 (3H, s),
30 3.06 (2H, d, J=13.0 Hz), 6.36-6.48 (1H, m), 7.06-7.17 (6H, m), 7.38-7.49 (4H, m), 7.73 (1H, d, J=15.0 Hz).

IR (KBr) 3048, 1672, 1606, 1541, 1512, 1348, 1151, 804 cm^{-1}

Elemental Analysis for $\text{C}_{26}\text{H}_{28}\text{NO}_2\text{SP}$

Calcd. C, 69.47 ; H, 6.28 ; N, 3.12 ; P, 6.89 :

35 Found. C, 69.48 ; H, 6.23 ; N, 3.20 ; P, 7.17.

Working Example 210 (Production of Compound 210)

To a solution of (E)-3-[5-(4-methylphenyl)furan-2-yl]acrylic acid (200mg), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (212mg) and triethylamine (0.15ml) in DMF (10ml) was added diethyl cyanophosphate (0.16ml) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:50→1:25→1:10) to give (E)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-3-[5-(4-methylphenyl)furan-2-yl]acrylic amide (Compound 210) (87mg) as brown amorphous. ¹H-NMR (200MHz, CDCl₃) δ 1.53-1.85 (4H, m), 2.21 (3H, s), 2.38 (3H, s), 2.54-2.72 (1H, m), 3.31-3.44 (2H, m), 3.56 (2H, s), 3.98-4.11 (2H, m), 6.52 (1H, d, J=15.4 Hz), 6.67-6.69 (2H, m), 7.22 (2H, d, J=8.0 Hz), 7.29 (2H, d, J=8.4 Hz), 7.41 (1H, s), 7.48-7.64 (5H, m).

Working Example 211 (Production of Compound 211)

To a solution of (E)-3-[5-(4-methylphenyl)furan-2-yl]acrylic acid (150mg), 1-(4-aminobenzyl)-phosphorinane-1-oxide (161mg) and triethylamine (0.11ml) in DMF (10ml) was added diethyl cyanophosphate (0.12ml) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:10→1:5→1:4) to give (E)-N-(4-(pentamethylene)phosphorylmethylphenyl)-3-[5-(4-methylphenyl)furan-2-yl]acrylic amide (Compound 211) (53mg) as brown crystals. ¹H-NMR (200MHz, CDCl₃) δ 1.43-2.09 (10H, m), 2.39 (3H, s), 3.15 (2H, d, J=13.2 Hz), 6.58-6.70 (3H, m), 7.16-7.29 (4H, m), 7.48-7.65 (5H, m), 8.24-8.35 (1H, m). IR (KBr) 3292, 1672, 1614, 1541, 1512, 1489, 1412, 1335,

1244, 1120, 787 cm^{-1}

Working Example 212 (Production of Compound 212)

- Under nitrogen atmosphere, oxalyl chloride (0.16ml) was added to a solution of (E)-3-[4-(4-methylphenyl)-thiophen-2-yl]acrylic acid (300mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). To the solution were added triethylamine (0.4ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-aniline (298mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate 1:4), and recrystallized from ethanol to give pale yellow crystals, which were recrystallized from tetrahydrofuran-hexane to give (E)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-3-[4-(4-methylphenyl)thiophen-2-yl]acrylamide (Compound 212) (261mg) as pale yellow crystals.
- m.p. 188-190°C
- $^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.45-1.83 (4H, m), 2.20 (3H, s), 2.38 (3H, s), 2.55-2.73 (1H, m), 3.31-3.44 (2H, m), 3.56 (2H, s), 3.99-4.10 (2H, m), 6.38 (1H, d, $J=15.2$ Hz), 7.20-7.32 (5H, m), 7.41-7.58 (6H, m), 7.89 (1H, d, $J=15.2$ Hz).
- IR (KBr) 3329, 2954, 1668, 1608, 1554, 1512, 1412, 1360, 1342, 1254, 1174, 1159, 984, 816 cm^{-1}
- Elemental Analysis for $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_2\text{S} \cdot 1.0\text{H}_2\text{O}$
- Calcd. C, 69.80 ; H, 6.94 ; N, 6.03 ;
- Found. C, 69.94 ; H, 6.85 ; N, 5.98.
- Working Example 213 (Production of Compound 213)

Under nitrogen atmosphere, oxalyl chloride (0.08ml) was added to a solution of (E)-3-[4-(4-methylphenyl)-thiophen-2-yl]acrylic acid (150mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml). To the solution were added triethylamine (0.2ml) and 1-(4-aminobenzyl)-phosphorinane-1-oxide (150mg) at 0°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give (E)-N-(4-(penta-methylene)phosphorylmethylphenyl)-3-[4-(4-methyl-phenyl)thiophen-2-yl]acrylic amide (Compound 213) (138mg) as pale yellow crystals. m.p. 279°C (dec.)

¹H-NMR (200MHz, CDCl₃) δ 1.49-2.23 (10H, m), 2.38 (3H, s), 3.15 (2H, d, J=12.8 Hz), 6.61 (1H, d, J=15.2 Hz), 7.13-7.28 (4H, m), 7.38-7.57 (6H, m), 7.86 (1H, d, J=15.2 Hz), 9.09-9.20 (1H, m).

IR (KBr) 3392, 2935, 1672, 1618, 1543, 1512, 1336, 1250, 1161, 818 cm⁻¹

Elemental Analysis for C₂₆H₂₈NO₂SP · 0.3H₂O

Calcd. C, 68.64 ; H, 6.34 ; N, 3.08 ; P, 6.81 :

Found. C, 68.44 ; H, 6.30 ; N, 3.06 ; P, 6.65.

Working Example 214 (Production of Compound 214)

Under nitrogen atmosphere, oxalyl chloride (0.12ml) was added to a solution of 2-(4-methylphenyl)-7,8-dihydro-6H-cyclohepta[b]thiophene-5-carboxylic acid (250mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml).

To the solution were added triethylamine (0.25ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (215mg) at 0°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-2-(4-methylphenyl)-7,8-dihydro-6H-cyclohepta[b]thiophene-5-carboxamide (Compound 214) (319mg) as colorless crystals.

m.p. 201-203°C

¹H-NMR (200MHz, CDCl₃) δ 1.62-1.84 (4H, m), 2.06-2.18 (2H, m), 2.21 (3H, s), 2.36 (3H, s), 2.53-2.71 (1H, m), 2.79-2.87 (2H, m), 3.06-3.15 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.97-4.08 (2H, m), 7.08 (1H, s), 7.14-7.22 (3H, m), 7.30 (2H, d, J=8.8 Hz), 7.43 (2H, d, J=8.0 Hz), 7.50-7.56 (3H, m).

IR (KBr) 3311, 2943, 1649, 1518, 1408, 1311, 810 cm⁻¹

Elemental Analysis for C₂₀H₂₄N₂O₂S

Calcd. C, 74.04 ; H, 7.04 ; N, 5.76 ; S, 6.59 ;

Found. C, 73.92 ; H, 6.85 ; N, 5.70 ; S, 6.53.

Working Example 215 (Production of Compound 215)

To a solution of (E)-3-[5-(4-methylphenyl)pyridin-3-yl]acrylic acid (150mg), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (168mg) and triethylamine (0.10ml) in DMF (10ml) was added diethyl cyanophosphate (0.12ml) at 0°C, and the mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure. To the residue was added water, the mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:2) to give (E)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-3-[5-(4-methylphenyl)pyridin-3-yl]acrylic amide (Compound 215) (24mg) as yellow solid.

¹H-NMR (200MHz, CDCl₃) δ 1.66-1.83 (4H, m), 2.21 (3H, s), 2.43 (3H, s), 2.53-2.74 (1H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 3.99-4.10 (2H, m), 6.69 (1H, d, J=15.5 Hz), 7.24-7.37 (4H, m), 7.41-7.63 (5H, m), 7.82 (1H, d, J=15.5 Hz), 7.95-8.01 (1H, m), 8.74 (1H, d, J=1.8 Hz), 8.81 (1H, d, J=2.2 Hz).

IR (KBr) 3242, 3190, 1678, 1606, 1545, 1514, 1348, 976, 816 cm⁻¹

Working Example 216 (Production of Compound 216)

To a solution of 6-(4-methylphenyl)-2-methylquinoline-3-carboxylic acid (120mg) and 1-hydroxybenzotriazole (88mg) in DMF (5ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (125mg) at room temperature, and the mixture was stirred for 2 hours. To the mixture was added a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (105mg) and triethylamine (0.2ml) in DMF (5ml), and the mixture was stirred for 18 hours and concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:2), and recrystallized from ethyl acetate-hexane to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-6-(4-methylphenyl)-2-methylquinoline-3-carboxamide (Compound 216) (82mg) as pale yellow crystals.

m.p. 157-160°C

¹H-NMR (200MHz, CDCl₃) δ 1.49-1.85 (4H, m), 2.23 (3H, s), 2.43 (3H, s), 2.54-2.76 (1H, m), 2.89 (3H, s), 3.31-3.47

(2H, m), 3.60 (2H, s), 4.00-4.11 (2H, m), 7.25-7.41 (4H, m), 7.55-7.71 (4H, m), 7.83 (1H, br s), 7.88 (1H, d, $J=1.8$ Hz), 8.01 (1H, dd, $J=8.8, 1.8$ Hz), 8.09 (1H, d, $J=8.8$ Hz), 8.21 (1H, s).

- 5 IR (KBr) 3311, 2958, 1657, 1520, 1313, 110, 847, 812 cm^{-1}
Elemental Analysis for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_2 \cdot 0.3\text{H}_2\text{O}$
Calcd. C, 76.76 ; H, 6.98 ; N, 8.66 :
Found. C, 76.68 ; H, 7.07 ; N, 8.80.

Working Example 217 (Production of Compound 217)

- 10 In THF (20ml) was dissolved 7-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid (1.00g), and to the solution were added oxalyl chloride ($523\mu\text{l}$) and a drop of DMF. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was
15 dissolved in THF (20ml), and to the solution were added 1-(3-aminobenzyl)piperidine (837mg) and triethylamine ($673\mu\text{l}$) at room temperature. The reaction mixture was stirred at room temperature for 2 hours, and to the mixture was added water (100ml). The mixture was extracted with ethyl acetate.
20 The organic layer was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropylether to give 7-phenyl-N-[3-(piperidinomethyl)phenyl]-3,4-dihydro-
25 naphthalene-2-carboxamide (Compound 217) (1.29g) as pale yellow crystals.

mp 152-153°C

Elemental Analysis for $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O} \cdot 0.1\text{H}_2\text{O}$

Calcd: C, 82.08; H, 7.17; N, 6.60.

- 30 Found: C, 81.97; H, 7.27; N, 6.47.

IR (KBr) cm^{-1} : 3373, 2933, 1645, 1543, 1487, 1439, 770, 696

^1H NMR (200MHz, CDCl_3) δ : 1.35-1.70 (6H, m), 2.32-2.45 (4H, m), 2.65-2.80 (2H, m), 2.92-3.03 (2H, m), 3.48 (2H, s), 7.08 (1H, d, $J=7.6\text{Hz}$), 7.25-7.50 (10H, m), 7.52-7.67 (3H, m).

- 35 Working Example 218 (Production of Compound 218)

In DMF (3ml) was dissolved 7-phenyl-N-[3-(piperidino-

- methyl)phenyl]-3,4-dihydronaphthalene-2-carboxamide (200mg), and to the mixture was added methyl iodide (88 μ l). The mixture was stirred at room temperature for 15 hours and concentrated under reduced pressure. The residue
- 5 was recrystallized from methanol-ethyl acetate to give 1-methyl-1-[3-(7-phenyl-3,4-dihydronaphthalene-2-carboxamido)benzyl]-piperidinium iodide (Compound 218) (211mg) as colorless crystals.
mp 208-209°C
- 10 Elemental Analysis for $C_{26}H_{23}N_2OI$
Calcd: C, 63.83; H, 5.89; N, 4.96.
Found: C, 63.58; H, 5.89; N, 4.95.
IR (KBr) cm^{-1} : 3450, 1657, 1520, 1483, 1439, 1250, 1215, 766, 702
- 15 1H NMR (200MHz, DMSO- d_6) δ : 1.40-2.00 (6H, m), 2.55-2.70 (2H, m), 2.80-3.00 (5H, m), 3.20-3.40 (4H, m), 4.57 (2H, s), 7.20-7.82 (12H, m), 8.03 (1H, s), 10.14 (1H, s).
Working Example 219 (Production of Compound 219)
To a solution of 2-(4-methylphenyl)-6,7-dihydro-
- 20 5H-benzocycloheptene-8-carboxylic acid (0.2g) in dichloromethane (5ml) were added oxalyl chloride (0.19ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved
- 25 in tetrahydrofuran. The mixture was added to a solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.17g) and triethylamine (0.3ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was
- 30 evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and precipitated crude
- 35 crystal was recrystallized from ethyl acetate-hexane to give 2-(4-methylphenyl)-N-(4-((N-tetrahydropyran-4-yl)-N-

methyl-amino)methyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 219) (0.29g) as colorless crystals.

mp 161-162°C.

- 5 ¹H-NMR(δ ppm, CDCl₃): 1.59-1.77 (4H, m), 2.13-2.21 (2H, m), 2.21 (3H, s), 2.40 (3H, s), 2.55-2.75 (3H, m), 2.86-2.92 (2H, m), 3.37 (2H, dt, J=2.8, 10.9Hz), 3.57 (2H, s), 4.01-4.07 (2H, m), 7.21-7.33 (4H, m), 7.41-7.58 (7H, m), 7.63 (1H, s).

- 10 IR(KBr) ν: 2938, 1651cm⁻¹.

Anal. for C₃₂H₃₆N₂O₂:

Calcd. C, 79.97; H, 7.55; N, 5.83.

Found C, 79.63; H, 7.43; N, 5.64.

Working Example 220 (Production of Compound 220)

- 15 A solution of 2-(4-methylphenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.11g) and methyl iodide (0.02ml) in dimethylformamide (4ml) was stirred at room temperature over night. The solvent was
- 20 evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which was recrystallized from ethanol-ethyl acetate to give N,N-dimethyl-N-(4-((2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl)carbonyl)aminobenzyl)-N-(4-
- 25 tetrahydropyranyl)ammonium iodide (Compound 220) (0.13g) as pale yellow crystals.

mp 157-158°C.

- ¹H-NMR(δ ppm, DMSO-d₆): 1.80-2.20 (6H, m), 2.35 (3H, s), 2.64 (2H, t, J=6.6Hz), 2.80-2.88 (2H, m), 2.88 (6H, s), 3.33-3.40 (2H, m), 3.50-3.65 (1H, m), 4.02-4.09 (2H, m), 4.47 (2H, s), 7.26-7.37 (4H, m), 7.50-7.60 (5H, m), 7.66 (1H, s), 7.88 (2H, d, J=8.8Hz), 10.22 (1H, s).

IR(KBr) ν: 1659cm⁻¹.

Anal. for C₃₃H₃₉IN₂O₂·0.5H₂O:

- 35 Calcd. C, 62.76; H, 6.38; N, 4.44.

Found C, 62.69; H, 6.38; N, 4.21.

Working Example 221 (Production of Compound 221)

A solution of 7-(4-piperidinophenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.2g) and methyl iodide (0.025ml) in dimethylformamide (5ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. Precipitated crude crystal was filtered, which were recrystallized from ethanol-ethyl acetate to give dimethyl(N-(7-(4-piperidinophenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)-4-tetrahydropyranylammonium iodide (Compound 221) (0.1g) as yellow crystals.
mp 189-190°C.

¹H-NMR (δ ppm, DMSO-d₆): 1.50-1.70 (6H, m), 1.75-2.00 (2H, m), 2.05-2.25 (2H, m), 2.88 (6H, s), 2.99 (2H, br), 3.16-3.19 (4H, m), 3.26-3.33 (2H, m), 3.50-1.70 (1H, m), 4.01-4.15 (2H, m), 4.29 (2H, br), 4.47 (2H, s), 7.00 (2H, d, J=8.8Hz), 7.03 (1H, d, J=8.4Hz), 7.35 (1H, s), 7.50-7.57 (5H, m), 7.68 (1H, d, J=2.6Hz), 7.86 (2H, d, J=8.4Hz), 10.19 (1H, s).
IR(KBr) ν: 2936, 1659cm⁻¹.

Anal. for C₃₆H₄₄IN₃O₇·H₂O:

Calcd. C, 60.76; H, 6.51; N, 5.90.

Found C, 60.57; H, 6.60; N, 5.85.

Working Example 222 (Production of Compound 222)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.3g) in dichloromethane (10ml) were added oxalyl chloride (0.28ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 4-(N-methyl-N-(tetrahydrothiopyran-4-yl)-aminomethyl)aniline (0.26g) and triethylamine (0.5ml) in tetrahydrofuran (20ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature for 7 hours. The solvent was evaporated, and to the residue was

added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was
5 evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-tetrahydrothiopyran-4-yl-N-methyl)amino-methyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-
10 carboxamide (Compound 222) (0.47g) as colorless crystals. mp 180-181°C.

¹H-NMR(δ ppm, CDCl₃): 1.60-1.85 (2H, m), 2.10-2.15 (2H, m), 2.21 (3H, s), 2.39 (3H, s), 2.40-2.50 (1H, m), 2.66-2.72 (4H, m), 3.08 (2H, t, J=4.6Hz), 3.57 (2H, s), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.0Hz), 7.31 (2H, d, J=8.4Hz), 7.43-7.57 (7H, m).
15 IR(KBr) ν: 2934, 1653cm⁻¹.

Anal. for C₃₁H₃₄N₂O₂S:

Calcd. C, 74.66; H, 6.87; N, 5.62.

20 Found C, 74.46; H, 6.72; N, 5.42.

Working Example 223 (Production of Compound 223)

A solution of N-(4-((N-tetrahydrothiopyran-4-yl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.11g) and methyl
25 iodide (0.025ml) in dimethylformamide (5ml) was stirred at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (chloroform/methanol) to give dimethyl-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-amino-
30 benzyl)-4-tetrahydrothiopyranylammonium iodide (Compound 223) (0.09g) as colorless crystals. mp 185-186°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 1.75-2.00 (2H, m), 2.34 (3H, s), 2.55-2.75 (4H, m), 2.75-2.85 (2H, m), 2.90 (6H, s), 3.00 (2H, br), 3.14-3.25 (1H, m), 4.31 (2H, br), 4.47 (2H, s),
35 7.07 (1H, d, J=8.4Hz), 7.27 (2H, d, J=7.8Hz), 7.36 (1H, s),

7.50-7.59 (5H, m), 7.74 (1H, d, $J=2.2\text{Hz}$), 7.86 (2H, d, $J=8.8\text{Hz}$), 10.19 (1H, s).

IR(KBr) ν : 2901, 1659 cm^{-1} .

Anal. for $\text{C}_{32}\text{H}_{37}\text{N}_5\text{O}_2\text{SI}\cdot\text{H}_2\text{O}$:

5 Calcd. C, 58.36; H, 5.97; N, 4.25.

Found C, 58.62; H, 6.04; N, 4.29.

Working Example 224 (Production of Compound 224)

To a solution of 2-(4-piperidinophenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.45g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.31g) and 1-hydroxybenzotriazole (0.18g) in dimethylformamide (20ml) was added 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydro-chloride (0.37g) under ice-cooling. Under nitrogen atmosphere, the mixture was warmed to room temperature. To the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.54ml), and the mixture was stirred over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 2-(4-piperidinophenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-6,7-dihydro-5H-benzocyclohepten-8-carboxamide (Compound 224) (0.44g) as pale orange crystals.

30 mp 170-171 $^{\circ}\text{C}$.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.59-1.65 (2H, m), 1.65-1.80 (8H, m), 2.05-2.21 (2H, m), 2.21 (3H, s), 2.55-2.68 (1H, m), 2.71 (2H, t, $J=6.3\text{Hz}$), 2.84-2.90 (2H, m), 3.19-3.24 (4H, m), 3.37 (2H, dt, $J=2.8, 11.2\text{Hz}$), 4.01-4.11 (2H, m), 7.00 (2H, d, $J=8.8\text{Hz}$), 7.20 (1H, d, $J=7.6\text{Hz}$), 7.31 (2H, d, $J=8.4\text{Hz}$), 7.41-7.51 (4H, m), 7.56 (2H, d, $J=8.4\text{Hz}$), 7.63 (1H, s).

IR(KBr) ν : 2936, 1661 cm^{-1} .

Anal. for $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_2 \cdot 0.2\text{H}_2\text{O}$:

Calcd. C, 78.14; H, 7.91; N, 7.59.

Found C, 78.09; H, 7.93; N, 7.55.

5 Working Example 225 (Production of Compound 225)

A solution of 2-(4-piperidinophenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methylamino)methyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.2g) and methyl iodide (0.025ml) in dimethylformamide (10ml) was
10 stirred at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (chloroform/methanol) to give crude crystals, which were recrystallized from ethanol-hexane to give dimethyl-
15 (N-(2-(4-piperidinophenyl)-6,7-dihydro-5H-benzocycloheptene-8-carbonyl)-4-aminobenzyl)-4-tetrahydropyranylammonium iodide (Compound 225) (0.15g) as pale brown crystals.

mp 177-178 $^{\circ}\text{C}$.

$^1\text{H-NMR}$ (δ ppm, $\text{DMSO}-d_6$): 1.50-1.70 (6H, m), 1.80-1.95 (2H, m),
20 2.00-2.10 (2H, m), 2.10-2.20 (2H, m), 2.60-2.70 (2H, m), 2.75-2.87 (2H, m), 2.88 (6H, s), 3.14-3.24 (6H, m), 3.53-3.65 (1H, m), 4.00-4.15 (2H, m), 4.46 (2H, s), 7.00 (2H, d, $J=8.8\text{Hz}$), 7.26 (1H, d, $J=8.0\text{Hz}$), 7.36 (1H, s), 7.46-7.62 (6H, m), 7.87 (2H, d, $J=8.8\text{Hz}$), 10.22 (1H, s).

25 IR(KBr) ν : 2934, 1655 cm^{-1} .

Anal. for $\text{C}_{37}\text{H}_{46}\text{IN}_3\text{O}_2 \cdot \text{H}_2\text{O}$:

Calcd. C, 62.62; H, 6.82; N, 5.92.

Found C, 62.32; H, 6.71; N, 5.92.

Working Example 226 (Production of Compound 226)

30 Under nitrogen atmosphere, oxalyl chloride (0.05ml) was added to a solution of 7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (80.6mg) in tetrahydrofuran (10ml) at room temperature. To the mixture was added a drop of DMF, and the mixture was stirred for
35 1 hour. Under reduced pressure, the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml). To the

- solution were added triethylamine (0.1ml) and 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (62.5mg) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to vigorously stirred water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 226) (85mg) as colorless crystals. m.p. 180-186°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.53-1.81 (4H, m), 2.21 (3H, s), 2.52 (3H, s), 2.54-2.73 (1H, m), 3.08 (2H, t, J=4.6 Hz), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.98-4.10 (2H, m), 4.36 (2H, t, J=4.6 Hz), 7.06 (1H, d, J=8.4 Hz), 7.23-7.36 (4H, m), 7.41-7.63 (8H, m).
- IR (KBr) 3319, 2947, 1645, 1516, 1485, 1315, 1248, 1140, 1086, 812 cm⁻¹
- Elemental Analysis for C₃₁H₃₄N₂O₃S · 0.2H₂O
Calcd. C, 71.84 ; H, 6.69 ; N, 5.40 ; S, 6.19 ;
Found. C, 71.75 ; H, 6.70 ; N, 5.38 ; S, 6.24.
- Reference Example 49
- To 3-bromocinnamic acid (2.0g) were added thionyl chloride (25ml) and dimethylformamide (catalytic amount), and the mixture was refluxed for 1.5 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a suspension of 1-(4-aminobenzyl)piperidine (1.7g) and diisopropylethylamine (4ml) in tetrahydrofuran (5ml) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and

saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give
5 crude crystals, which were recrystallized from ethyl acetate-hexane to give 1-(4-(3-bromocinnamoylamino)-benzyl)piperidine (1.8g) as colorless crystals.
mp 144-145°C.

¹H-NMR(δ ppm, CDCl₃): 1.37-1.49 (2H, m), 1.52-1.63 (4H, m),
10 2.34-2.39 (4H, m), 3.45 (2H, s), 6.54 (1H, d, J=15.5Hz),
7.21-7.33 (3H, m), 7.41-7.57 (5H, m), 7.67 (1H, d, J=15.5Hz),
7.69 (1H, s).

IR(KBr) ν: 3270, 2934, 1663cm⁻¹.

Anal. for C₂₁H₂₃BrN₂O · 0.2H₂O:

15 Calcd. C, 62.60; H, 5.85; N, 6.95.

Found C, 62.67; H, 5.79; N, 6.93.

Reference Example 50

To 3-phenylcinnamic acid (0.24g) were added thionyl chloride (10ml) and dimethylformamide (catalytic amount),
20 and the mixture was refluxed for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a suspension of 2-(4-aminobenzyl)-1,3,2-dioxaphosphorinane-2-oxide (0.2g) and diisopropylethylamine (0.8ml) in tetrahydro-
25 furan (20ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water.

The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride
30 solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and precipitated crude crystal was recrystallized from ethanol-hexane to give 2-(4-(3-phenylcinnamoylamino)-benzyl)-1,3,2-dioxaphosphorinane-2-oxide (0.32g) as
35 colorless crystals.
mp 204-205°C.

¹H-NMR(δ ppm, CDCl₃): 1.84-1.88 (2H, m), 3.24 (2H, d, J=21.2Hz), 4.07-4.22 (2H, m), 4.34-4.44 (2H, m), 6.74 (1H, d, J=15.8Hz), 7.23 (2H, dd, J=2.6, 8.8Hz), 7.38-7.63 (10H, m), 7.77 (1H, s), 7.81 (1H, d, J=15.8Hz), 8.16 (1H, br).

5 IR(KBr) ν: 3059, 1680cm⁻¹.

Anal. for C₂₅H₂₄NO₄P:

Calcd. C, 69.28; H, 5.58; N, 3.23.

Found C, 68.82; H, 5.58; N, 3.30.

Reference Example 51

10 To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.15g) in dichloromethane (7ml) were added oxalyl chloride (0.14ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours.

15 The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a solution of 2-(4-aminobenzyl)-1,3,2-dioxaphosphorinane-2-oxide (0.13g) and triethylamine (0.23ml) in tetrahydrofuran (20ml), under ice-cooling. Under nitrogen atmosphere,

20 the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate.

25 Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-ethanol-hexane to give 2-(4-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonylamino)benzyl)-1,3,2-dioxaphosphorinane-2-oxide (0.23g) as colorless crystals.

30 mp 268-269°C.

¹H-NMR(δ ppm, CDCl₃): 1.75-1.87 (2H, m), 2.40 (3H, s), 3.09 (2H, t, J=4.5Hz), 3.24 (2H, d, J=21.6Hz), 4.02-4.19 (2H, m), 4.34-4.50 (4H, m), 7.06 (1H, d, J=8.4Hz), 7.23-7.32 (4H, m), 7.44-7.60 (6H, m), 7.81 (1H, s).

35 IR(KBr) ν: 1652cm⁻¹.

Anal. for C₂₈H₂₈NO₅P:

Calcd. C, 68.70; H, 5.77; N, 2.86.

Found C, 68.54; H, 5.71; N, 2.86.

Reference Example 52

A suspension of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.18g), 1-t-butoxycarbonyl-4-methylaminopiperidine (0.19g) and potassium carbonate (0.18g) in dimethylformamide (10ml) was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-(1-t-butoxycarbonylpiperidin-4-yl)-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.25g) as colorless crystals.
mp 203-204°C.

¹H-NMR (δ ppm, CDCl₃): 1.37-1.70 (4H, m), 1.46 (9H, s), 1.77-1.83 (2H, m), 2.19 (3H, s), 2.39 (3H, s), 2.52-2.74 (3H, m), 3.08 (2H, t, J=4.6Hz), 3.56 (2H, s), 4.18 (1H, br), 4.36 (2H, t, J=4.6Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.33 (5H, m), 7.43-7.61 (6H, m).

IR (KBr) ν: 2977, 2933, 1695, 1668 cm⁻¹.

Anal. for C₂₆H₃₀N₂O₄:

Calcd. C, 74.33; H, 7.45; N, 7.22.

Found C, 74.00; H, 7.41; N, 7.26.

Reference Example 53

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.6g) in dichloromethane (25ml) were added oxalyl chloride (0.56ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a

solution of (4-aminophenyl)[1-(tert-butoxycarbonyl)-
piperidin-2-yl]methanone (0.72g) and triethylamine (0.9ml)
in tetrahydrofuran (50ml), under ice-cooling. Under
nitrogen atmosphere, the mixture was stirred at room
5 temperature over night. The solvent was evaporated, and to
the residue was added water. The mixture was extracted with
ethyl acetate. The organic layer was washed with water and
saturated sodium chloride solution, and dried with anhydrous
magnesium sulfate. Under reduced pressure, the solvent was
10 evaporated to give crude crystals, which were recrystallized
from ethyl acetate-hexane to give N-(4-(1-(tert-
butoxycarbonyl)piperidin-2-ylcarbonyl)-phenyl)-7-(4-
methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(1.1g) as pale yellow crystals.

15 mp 223-224°C.

¹H-NMR (δ ppm, CDCl₃): 1.44 (9H, br), 1.44-1.65 (4H, m),
1.70-1.95 (1H, m), 2.00-2.20 (1H, m), 2.39 (3H, s), 3.08
(2H, t, J=4.4Hz), 5.60 (1H, br), 7.06 (1H, d, J=8.4Hz), 7.25
(2H, d, J=11.8Hz), 7.44-7.53 (4H, m), 7.65 (1H, br), 7.69
20 (1H, br), 7.82 (1H, br), 7.94 (2H, d, J=8.8Hz).

IR(KBr) ν: 2942, 1678cm⁻¹.

Anal. for C₃₅H₃₆N₂O₃·0.3H₂O:

Calcd. C, 73.48; H, 6.80; N, 4.90.

Found C, 73.51; H, 6.60; N, 4.68.

25 Reference Example 54

To a mixture of 3-bromobenzaldehyde (10g) and
methoxy-carbonylmethylenetriphenylphosphine (20g) was
added toluene (150ml), and the mixture was refluxed under
nitrogen atmosphere for 2 hours. The solvent was evaporated,
30 and the organic layer was washed with water and saturated
sodium chloride solution, and dried with anhydrous magnesium
sulfate. Under reduced pressure, the solvent was
evaporated, and the residue was purified with silica gel
column (ethyl acetate/hexane) to give methyl 3-bromo-
35 cinnamate (10.7g) as colorless crystals.

¹H-NMR (δ ppm, CDCl₃): 3.82 (3H, s), 6.44 (1H, d, J=16.0Hz),

7.27 (1H, d, J=15.6Hz), 7.43-7.54 (2H, m), 7.62 (1H, d, J=16.0Hz), 7.66-7.68 (1H, m).

IR(KBr) ν : 1734, 1717 cm^{-1} .

Anal. for $\text{C}_{10}\text{H}_9\text{BrO}_2$:

5 Calcd. C, 49.82; H, 3.76.

Found C, 49.90; H, 3.90.

Reference Example 55

In a solution of methanol (200ml) and 2N sodium hydroxide (50ml) was dissolved methyl 3-bromocinnamate (10.7g), and the mixture was stirred at room temperature over night, concentrated and neutralized with 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 3-bromophenylcinnamic acid (9.2g) as colorless crystals.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 6.45 (1H, d, J=15.8Hz), 7.28 (1H, t, J=7.7Hz), 7.45-7.56 (2H, m), 7.67-7.75 (2H, m).

20 IR(KBr) ν : 1688 cm^{-1} .

Anal. for $\text{C}_9\text{H}_7\text{BrO}_2$:

Calcd. C, 47.61; H, 3.11.

Found C, 47.57; H, 3.10.

Reference Example 56

25 A suspension of methyl 3-bromocinnamate (3.8g), phenyl borate (2.0g), 1M potassium carbonate (20ml) and ethanol (10ml) in toluene (100ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the reaction mixture was added tetrakis(triphenyl)-phosphinepalladium (0.9g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (3.6g), 1.8g of which was dissolved in a solution of methanol

(100ml) and 1N sodium hydroxide (20ml). The mixture was stirred at room temperature over night, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 3-phenylcinnamic acid (1.5g) as colorless crystals.

¹H-NMR(δ ppm, CDCl₃): 6.54 (1H, d, J=16.0Hz), 7.39-7.67 (8H, m), 7.76-7.77 (1H, m), 7.87 (1H, d, J=16.0Hz).

IR(KBr) ν 1709cm⁻¹.

Anal. for C₁₅H₁₂O₂:

Calcd. C, 80.34; H, 5.39.

Found C, 80.62; H, 5.40.

15 Reference Example 57

To 4-nitrobenzylphosphonic acid (0.5g) were added thionyl chloride (5ml) and dimethylformamide (catalytic amount), and the mixture was refluxed under nitrogen atmosphere for 4 hours. The solvent was evaporated, and to the residue was added toluene. The solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the mixture was cooled to -78°C under nitrogen atmosphere. To the mixture was dropwise added dimethylpropanediamine (0.3ml) dissolved in tetrahydrofuran (2ml) and then triethylamine (1.6ml), and the mixture was gradually warmed to room temperature and stirred at room temperature over night. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give colorless crystals, which were dissolved in ethanol (15ml). To the mixture was added 10% palladium on carbon (0.04g), and catalytic hydrogenation was carried out at room temperature for 3.5 hours. The catalyst was filtered off, and the solvent was evaporated to give 2-(4-aminobenzyl)-1,3-dimethyl-1,3,2-diazaphosphorinane-2-oxide (0.3g) as colorless crystals.

¹H-NMR(δ ppm, CDCl₃): 1.09-1.27 (1H, m), 1.68-1.85 (1H, m),

2.65 (3H, s), 2.69 (3H, s), 2.72-3.01 (4H, m), 3.08 (2H, d, $J=17.4\text{Hz}$), 6.65 (2H, d, $J=8.1\text{Hz}$), 6.96 (2H, dd, $J=2.4$, 8.1Hz).

IR(KBr) ν : 3339, 2897, 1615cm^{-1} .

5 Anal. for $\text{C}_{12}\text{H}_{20}\text{N}_3\text{OP} \cdot 0.3\text{H}_2\text{O}$:

Calcd. C, 55.72; H, 8.03; N, 16.24.

Found C, 55.69; H, 7.98; N, 16.13.

Reference Example 58

To 4-nitrobenzylphosphonic acid (0.5g) were added
10 thionyl chloride (5ml) and dimethylformamide (catalytic amount), and the mixture was refluxed for 3 hours under nitrogen atmosphere. The solvent was evaporated, and to the residue was added toluene. The solvent was evaporated. The residue was dissolved in tetrahydrofuran (5ml), and the
15 mixture was cooled to -78°C under nitrogen atmosphere. To the mixture was dropwise added dimethylethylenediamine (0.25ml) dissolved in tetrahydrofuran (2ml), and then triethylamine (1.5ml), and the mixture was gradually warmed to room temperature and stirred at room temperature over
20 night. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give colorless crystals, which were dissolved in ethanol (15ml). To the mixture was added 10% palladium on carbon (0.05g), and catalytic hydrogenation
25 was carried out at room temperature for 3 hours. The catalyst was filtered off, and the solvent was evaporated to give 2-(4-aminobenzyl)-1,3-dimethyl-1,3,2-diazaphosphorane-2-oxide (0.3g) as yellow crystals.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 2.61 (3H, s), 2.63-2.71 (2H, m), 2.66
30 (3H, s), 3.00-3.07 (2H, m), 3.13 (2H, d, $J=18.2\text{Hz}$), 6.63 (2H, d, $J=8.5\text{Hz}$), 6.97 (2H, dd, $J=2.4$, 8.5Hz).

IR(KBr) ν : 3341, 2895, 1632cm^{-1} .

Anal. for $\text{C}_{11}\text{H}_{18}\text{N}_3\text{OP} \cdot 0.5\text{H}_2\text{O}$:

Calcd. C, 53.22; H, 7.71; N, 16.93.

35 Found C, 53.23; H, 7.53; N, 16.83.

Reference Example 59

A suspension of 3-bromo-6,7,8,9-tetrahydro-5H-benzocycloheptan-5-one (4.6g; L. A. M. Cornelius and D. W. Combs, Synth. Commun. (1994), 24(19), 2777-2788), 4-methylphenyl borate (3.8g), 2M potassium carbonate (30ml) and ethanol(30ml) in toluene(100ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (1.5g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale brown oil (5.7g), to which were added sodium methoxide (6.2g) and dimethyl carbonate (100ml). The mixture was refluxed under nitrogen atmosphere for 8 hours and poured into 1N hydrochloric acid under ice-cooling. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give brown oil (5.5g), which was dissolved in dichloromethane (20ml). To the mixture was dropwise added sodium boron hydride dissolved in methanol, under ice-cooling. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and to the residue were added 1N sodium hydroxide (40ml), methanol (40ml) and diethylether (100ml). The mixture was heated to 50°C for 30 minutes and concentrated. To the residue was added 1N sodium hydroxide, and the mixture was extracted with water, washed with ethyl acetate and acidified with hydrochloric acid. The mixture was extracted with ethyl

acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was dissolved in Diglyme(20ml). To the mixture was added hydrochloric acid (5ml), and the mixture was heated to 100°C for 6 hours and poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.3g) as colorless crystals.

¹H-NMR(δ ppm, CDCl₃): 2.07-2.16 (2H, m), 2.40 (3H, s), 2.70 (2H, t, J=6.6Hz), 2.86-2.91 (2H, m), 7.21-7.28 (3H, m), 7.44-7.56 (4H, m), 7.91 (1H, s).

IR(KBr) ν: 2930, 1678cm⁻¹.

Anal. for C₁₅H₁₆O₂:

Calcd. C, 81.99; H, 6.52.

Found C, 81.64; H, 6.41.

Reference Example 60

In dimethylformamide (100ml) was added 4-bromothiophenol (25g). To the solution were added ethyl 4-bromobutyrate (30g) and potassium carbonate (36g), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and to the residue were added 1N sodium hydroxide (240ml) and methanol (120ml). The mixture was stirred at room temperature over night and concentrated. The residue was dissolved in water, and the mixture was washed with ethyl acetate. The aqueous layer was acidified with hydrochloric acid under ice-cooling. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous

magnesium sulfate. The solvent was evaporated to give colorless crystals (32g), to which was added polyphosphoric acid (250g), and the mixture was stirred at 100°C for 1 hour and poured into ice-water. The mixture was extracted with ethyl acetate. The organic layer was washed with water, sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give brown crystals (13.6g), to which were added sodium methoxide (14.2g) and dimethyl carbonate (200ml), and the mixture was refluxed under nitrogen atmosphere for 8 hours. Under ice-cooling, the mixture was poured into 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. the solvent was evaporated to give brown crystals (11.5g), which were dissolved in dichloromethane (100ml). To the mixture was dropwise added sodium boron hydride dissolved in methanol, under ice-cooling. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and to the residue were added 1N sodium hydroxide (100ml), methanol (100ml) and diethylether (500ml). The mixture was stirred at room temperature for 1.5 hours and concentrated. To the residue was added 1N sodium hydroxide, and the mixture was extracted with water, washed with diethylether and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was dissolved in Diglyme (100ml). To the mixture was added hydrochloric acid (20ml), and the mixture was heated to 110°C for 2.5 hours and poured into water. The mixture was extracted with

ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give colorless crystal (1.1g), 1g of which was suspended
5 dichloromethane (15ml). To the suspension were added oxalyl chloride (1ml) and dimethylformamide (catalytic amount) under ice-cooling, and the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The
10 mixture was dropwise added to a solution of 4-(tert-butyl dimethylsilyloxy)aniline (0.76g) and triethylamine (1.6ml) in tetrahydrofuran (20ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to
15 the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown oil (1.8g), to which were added
20 4-methylphenyl borate (0.5g), 1M potassium carbonate (15ml), ethanol (15ml) and toluene (500ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl-
phosphine)palladium (0.2g), and the mixture was refluxed over
25 night. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel
30 column (ethyl acetate/hexane) to give colorless crystals (1.3g), which were dissolved in ethyl acetate (50ml). To the mixture was added hydrochloric acid (5ml), and the mixture was stirred at room temperature for 1.5 hours, washed with sodium hydrogen carbonate solution, water, saturated
35 sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was

evaporated to give 7-(4-methylphenyl)-N-(4-hydroxy-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (1.0g) as colorless crystals.

¹H-NMR(δ ppm, CDCl₃): 2.40 (3H, s), 3.08 (2H, t, J=5.8Hz),
5 3.29 (2H, t, J=5.8Hz), 4.69 (2H, s), 7.24-7.28 (2H, m),
7.35-7.62 (10H, m), 7.71 (1H, br).

IR(KBr) ν: 3314, 2928, 1649cm⁻¹.

Anal. for C₂₃H₂₃NO₂S·0.2H₂O:

Calcd. C, 74.12; H, 5.82; N, 3.46.

10 Found C, 74.10; H, 5.65; N, 3.47.

Reference Example 61

In dimethylformamide (100ml) was dissolved 4-bromo-phenol (17.3g). To the solution were added ethyl 4-bromo-butyrates (21.2g) and potassium carbonate (25g), and the
15 mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was
20 evaporated, and to the residue were added 3N sodium hydroxide (100ml) and methanol (60ml). The mixture was stirred at 70°C for 30 minutes and concentrated. The residue was dissolved in water, and the mixture was washed with diethylether. The aqueous layer was acidified with hydrochloric acid under
25 ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give colorless crystal (23.9g), to 10g of which was added polyphosphoric
30 acid (120g). The mixture was stirred at 100°C for 45 minutes and poured into ice-water. The mixture was extracted with ethyl acetate. The organic layer was washed with water, sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium
35 sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to

give 7-bromo-2,3,4,5-tetrahydrobenzoxepin-5-one as yellow oil (6.5g).

¹H-NMR(δ ppm, CDCl₃): 2.15-2.29 (2H, m), 2.89 (2H, t, J=7.0Hz), 4.24 (2H, t, J=6.6Hz), 6.97 (1H, d, J=8.8Hz), 7.50 (1H, dd, J=2.6, 8.1Hz), 7.87 (1H, d, J=2.6Hz).
IR(neat) ν : 2969, 1686cm⁻¹.

Reference Example 62

To 7-bromo-2,3,4,5-tetrahydrobenzoxepin-5-one (6.5g) were added 4-methylphenyl borate (4.1g), 2M potassium carbonate (30ml), ethanol(30ml) and toluene(100ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (1.3g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow crystal (5.7g), to 3.6g of which was added sodium methoxide (3.9g) and dimethyl carbonate (50ml). Under nitrogen atmosphere, the mixture was refluxed for 8 hours and poured into 1N hydrochloric acid under ice-cooling. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystal (3.5g), 1.8g of which was dissolved in dichloromethane (25ml). To the mixture was dropwise added sodium boron hydride dissolved in methanol, under ice-cooling. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. To the residue

were added 1N sodium hydroxide (50ml), methanol (25ml) and diethylether (25ml), and the mixture was stirred at room temperature for 30 minutes and concentrated. To the mixture was added 1N sodium hydroxide, and the mixture was extracted
5 with water, washed with diethylether and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was
10 dissolved in Diglyme (25ml). To the mixture was added hydrochloric acid (5ml), and the mixture was heated at 100°C for 40 minutes and poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with
15 anhydrous magnesium sulfate. The solvent was evaporated to give 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (1.2g) as colorless crystals.
mp 255-256°C.

¹H-NMR(δ ppm, CDCl₃): 2.40 (3H, s), 3.02 (2H, t, J=4.6Hz),
20 4.33 (2H, t, J=4.6Hz), 7.05 (1H, d, J=8.6Hz), 7.24 (2H, d, J=8.2Hz), 7.46 (2H, d, J=8.2Hz), 7.47-7.56 (2H, m), 7.78 (1H, s).

IR(KBr) ν: 2996, 1694cm⁻¹.

Anal. for C₁₈H₁₆O₃:

25 Calcd. C, 77.12; H, 5.75.

Found C, 76.91; H, 5.75.

Reference Example 63

In dichloromethane (10ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid
30 (1.0g) and to the suspension were added oxalyl chloride (1ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 3 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran. The mixture was dropwise added to a
35 solution of 4-(tert-butyldimethyl-silyloxy)aniline (0.93g) and triethylamine (1.5ml) in tetrahydrofuran (15ml),

under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless oil (1.88g), which was dissolved in ethyl acetate(20ml). To the mixture was added hydrochloric acid (5ml), and the mixture was stirred at room temperature 1.5 hours. The mixture was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.9g), which was suspended in dichloromethane (60ml). To the suspension were added lithium chloride (0.1g) and triethylamine (1ml). To the mixture was dropwise added methanesulfonylchloride (0.3ml) under ice-cooling, and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give N-(4-chloromethylphenyl)-7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.4g).

¹H-NMR(δ ppm, CDCl₃): 2.39 (3H, s), 3.08 (2H, t, J=4.6Hz), 4.36 (2H, t, J=4.6Hz), 4.59 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.22-7.26 (2H, m), 7.36-7.53 (6H, m), 7.60 (2H, d, J=8.4Hz), 7.65 (1H, s).

IR(KBr) ν: 3025, 1649cm⁻¹.

Reference Example 64

In tetrahydrofuran (50ml) were suspended p-nitro-phenethylbromide (2.3g) and sodium iodide (1.5g). To the suspension was added piperidine (4ml), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow oil (2.3g), which was dissolved in ethanol (50ml). To the mixture was added 10% palladium on carbon (0.23g), and catalytic hydrogenation was carried out at room temperature over night. The catalyst was filtered off, and the solvent was evaporated to give 1-(2-(4-aminophenyl)ethyl)-piperidine (2.0g) as yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.43-1.50 (2H, m), 1.56-1.67 (4H, m), 2.42-2.53 (6H, m), 2.67-2.75 (2H, m), 3.55 (2H, br), 6.62 (2H, d, $J=8.4\text{Hz}$), 6.99 (2H, d, $J=8.4\text{Hz}$).

IR(neat) ν : 2935, 1623 cm^{-1} .

Reference Example 65

To 5'-bromo-2'-hydroxyacetophenone (10g) were added 4-methylphenyl borate (6.7g), 2M potassium carbonate (70ml), ethanol (70ml) and toluene (200ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphinepalladium (2.1g), and the mixture was refluxed over night. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow crystal (7.4g), 2.3g of which was dissolved in pyridine (15ml). To the mixture was added benzoyl chloride (1.4ml), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated, and to the residue was added water.

The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give colorless crystals (3.0g), 2.9g of which was dissolved in pyridine (25ml). To the mixture was added potassium hydroxide (0.7g) little by little at 50°C. The mixture was stirred at 50°C for 1 hour, and the solvent was evaporated. To the residue was added 10% acetic acid under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow crystal (2.3g), to which was added sulfuric acid (0.37ml) and acetic acid (15ml). The mixture was refluxed for 1 hour and poured into ice-water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give colorless crystal (2.1g), which was dissolved in dimethylsulfoxide (150ml). To the mixture was dropwise added a solution which was prepared by adding a solution of trimethylsulfoxonium iodide (2.3g) in dimethylsulfoxide (60ml) dropwise to a suspension of sodium hydride (60%, 0.44g) in dimethylsulfoxide (10ml) and stirring the mixture under nitrogen atmosphere at room temperature for 40 minutes. The mixture was stirred at room temperature for 3 hours and further stirred at 50°C for 2 hours. The mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow crystals (1.7g), to which were added tributyltin hydride (2.1ml),

- 2,2'-azobis(isobutyro-nitrile) (0.64g) and toluene (50ml). The mixture was stirred under nitrogen atmosphere at 100°C for 1 hour, washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate.
- 5 Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.65g), to which were added sodium methoxide (0.54g) and dimethyl carbonate (25ml). The mixture was refluxed under nitrogen atmosphere
- 10 for 8 hours and poured into 1N hydrochloric acid under ice-cooling. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give pale brown oil
- 15 (0.76g), which was dissolved in dichloromethane (50ml). To the mixture was dropwise added the solution of sodium boron hydride in methanol at -10°C. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated extracted with ethyl acetate.
- 20 The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. To the residue were added 1N sodium hydroxide (20ml) and methanol (200ml), and the mixture was stirred at room temperature for 3 hours,
- 25 concentrated and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was dissolved in Diglyme (50ml),
- 30 and to the mixture was added hydrochloric acid (10ml). The mixture was stirred at 100°C for 30 minutes and poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The
- 35 solvent was evaporated to give 7-(4-methylphenyl)-2-phenyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.4g)

as colorless crystals.

mp 296-297°C.

¹H-NMR(δ ppm, CDCl₃): 2.40 (3H, s), 3.10-3.39 (2H, m), 5.02 (1H, dd, J=1.8, 8.8Hz), 7.10 (1H, d, J=8.4Hz), 7.12-7.27 (2H, m), 7.35-7.53 (8H, m), 7.58 (1H, d, J=2.2Hz), 7.86 (1H, d, J=2.0Hz).

IR(KBr) ν: 1673cm⁻¹.

Anal. for C₂₄H₂₀O₃·0.1H₂O:

Calcd. C, 80.47; H, 5.68.

10 Found C, 80.41; H, 5.73.

Reference Example 66

In 1,2-dichloroethane (100ml) were suspended p-nitrobenzylamine hydrochloride (7.5g), 4H-tetrahydropyran-4-one (4.0g) and triethylamine (5.6ml), and to the suspension was added sodium triacetoxy boron hydride (11.8g) under ice-cooling. The mixture was stirred under nitrogen atmosphere at room temperature for 5 hours. To the mixture were added 37% formalin (3.6ml) and sodium triacetoxy boron hydride (11.8g) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 4 hours. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown oil (10g), to which were added reduced iron (9g) and acetic acid (200ml). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (7.3g) as colorless crystals.

mp 93-94°C.

¹H-NMR(δ ppm, CDCl₃): 1.65-1.76 (4H, m), 2.19 (3H, s),
2.58-2.68 (1H, m), 3.36 (2H, dt, J=3.2, 11.3Hz), 3.48 (2H,
s), 3.60 (2H, br), 4.00-4.05 (2H, m), 6.65 (2H, d, J=8.4Hz),
5 7.09 (2H, d, J=8.4Hz).

IR(KBr) ν: 2952, 2844, 2788, 1613cm⁻¹.

Anal. for C₁₃H₂₀N₂O·0.1H₂O:

Calcd. C, 70.30; H, 9.17; N, 12.61.

Found C, 70.21; H, 8.85; N, 12.64.

10 Reference Example 67

In methanol (20ml) was dissolved ethyl levulinate (10g),
and to the mixture was added sodium boron hydride (0.7g)
at -78°C. The mixture was warmed to room temperature, and
to the mixture was added ammonium chloride solution. The
15 mixture was concentrated, extracted with diethylether, and
dried with anhydrous magnesium sulfate. The solvent was
evaporated to give colorless oil (9.3g), which was dissolved
in tetrahydrofuran (50ml). To the mixture was added
triethylamine (10.6ml) under ice-cooling, and to the mixture
20 was dropwise added methane-sulfonylchloride (4.9ml). The
mixture was warmed to room temperature, and the solvent was
evaporated. To the residue were added sodium iodide (11.4g)
and acetone (50ml), and the mixture was stirred at 50°C for
2 hours. The solvent was evaporated, and to the residue was
25 added ethyl acetate. The precipitate was filtered off, and
the solvent was evaporated. The residue was purified with
silica gel column (ethyl acetate/hexane) to give colorless
oil (7.0g), which was dissolved in dimethylformamide (20ml).
The mixture was dropwise added to a solution of methyl
30 5-bromosalicylate (1.8g) and sodium hydride (60%, 0.33g)
in dimethylformamide (20ml), under ice-cooling, and the
mixture was stirred at 50°C over night. The solvent was
evaporated, and to the residue was added water. The mixture
was extracted with ethyl acetate. The organic layer was
35 washed with water and saturated sodium chloride solution,
and dried with anhydrous magnesium sulfate. Under reduced

pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless oil (1.1g), which was dissolved in tetrahydrofuran (20ml). The mixture was dropwise added to a solution of lithium diisopropylamine, which was prepared by diisopropylamine (0.37g) and a solution of n-butyl lithium in hexane (1.6M, 2.1ml), in tetrahydrofuran, at -78°C. The mixture was stirred at room temperature under argon atmosphere over night and poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless oil (0.3g), which was dissolved in dichloromethane (25ml). The mixture was dropwise added to a solution of sodium boron hydride in methanol at -10°C. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was dissolved in dichloromethane (25ml). To the mixture was added triethylamine (0.74ml), and to the mixture was dropwise added methanesulfonylchloride (0.15ml) under ice-cooling. The mixture was stirred at room temperature under nitrogen atmosphere over night, washed with water and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.2g), to which were added 4-methylphenyl borate (0.1g), 1M potassium carbonate (2.5ml), ethanol (2.5ml) and toluene (15ml). The mixture was stirred under argon atmosphere at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (0.03g). The mixture was refluxed over night and extracted

with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.2g), to which were added 1N sodium hydroxide (5ml) and methanol (50ml). The mixture was refluxed for 30 minutes, concentrated, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-(4-methylphenyl)-2-methyl-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.2g) as colorless crystals.

mp 224-225°C.

¹H-NMR (δ ppm, CDCl₃): 1.53 (3H, d, J=6.2Hz), 2.40 (3H, s), 2.81 (1H, ddd, J=2.2, 8.8, 18.0Hz), 3.08 (1H, d, J=18.0Hz), 4.17-4.27 (1H, m), 7.04 (1H, d, J=8.2Hz), 7.24 (2H, d, J=7.4Hz), 7.44-7.52 (4H, m), 7.77 (1H, d, J=2.2Hz).

IR(KBr) ν: 2973, 1674cm⁻¹.

Anal. for C₁₉H₁₈O₃:

Calcd. C, 77.53; H, 6.16.

Found C, 77.60; H, 6.14.

Reference Example 68

In ethanol (10ml) and ethyl acetate (60ml) was dissolved 4-methylphenyl 4-nitrobenzyl sulfone (0.5g; G. Bram et al., Synthesis, 1987, 56-59). To the mixture was added 10% palladium on carbon (0.05g) and catalytic hydrogenation was carried out at room temperature over night. The catalyst was filtered off, and the solvent was evaporated to give 4-aminobenzyl 4-methylphenyl sulfone (0.4g) as colorless crystals.

¹H-NMR (δ ppm, CDCl₃): 2.42 (3H, s), 4.18 (2H, s), 6.56 (2H, d, J=8.4Hz), 6.86 (2H, d, J=8.4Hz), 7.24 (2H, d, J=8.2Hz), 7.52 (2H, d, J=8.2Hz).

IR(KBr) ν: 3443, 3370, 2926, 1612cm⁻¹.

Anal. for $C_{14}H_{15}NO_2S \cdot 0.2H_2O$:

Calcd. C, 63.47; H, 5.86; N, 5.29.

Found C, 63.63; H, 5.86; N, 5.09.

Reference Example 69

5 In 1,2-dichloroethane (50ml) were suspended cyclopentanone (1g), methylamine hydrochloride (1.6g) and triethylamine (3.4ml), and to the suspension was added sodium triacetoxy boron hydride (3.5g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room
10 temperature over night. The mixture was neutralized with sodium hydroxide, concentrated and extracted with water. The aqueous layer was washed with ethyl acetate. The aqueous layer was saturated with sodium chloride and extracted with diethylether. The organic layer was dried
15 with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give N-methylcyclopentylamine (0.5g) as colorless oil.

1H -NMR (δ ppm, $CDCl_3$): 1.21-1.86 (8H, m), 2.40 (3H, s), 2.94-3.01 (1H, m).

20 Reference Example 70

In 1,2-dichloroethane (50ml) were suspended cycloheptanone (2g), methylamine hydrochloride (3g) and triethylamine (6.2ml), and to the suspension was added sodium triacetoxy boron hydride (5.3g) under ice-cooling.
25 Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried
30 with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give N-methylcycloheptylamine (1.8g) as colorless oil.

1H -NMR (δ ppm, $CDCl_3$): 1.26-1.70 (10H, m), 1.77-1.89 (2H, m), 2.40 (3H, s), 2.47-2.58 (1H, m).

35 IR (KBr) ν : 2933, 2860 cm^{-1} .

Reference Example 71

In tetrahydrofuran (100ml) were added 4-amino-1-benzyl-piperidine (10g) and triethylamine (36ml), and to the mixture was dropwise added acetyl chloride (4.1ml) under ice-cooling. The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give colorless crystal (2.6g), which was dissolved in tetrahydrofuran (10ml). Under ice-cooling, borane methylsulfide (2.2ml) was dropwise added to the solution. Under nitrogen atmosphere, the mixture was refluxed for 5 hours. Under ice-cooling, methanol (10ml) was added to the mixture, and the mixture was stirred at room temperature for 1 hour. To the mixture was added 4N hydrochloric acid-ethyl acetate, and the mixture was refluxed for 1 hour. The solvent was evaporated, and to the residue was added 1N sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-ethylamino-1-benzylpiperidine (1.2g) as colorless oil.

¹H-NMR(δ ppm, CDCl₃): 1.10 (3H, t, J=7.2Hz), 1.28-1.47 (2H, m), 1.82-1.88 (2H, m), 1.95-2.07 (2H, m), 2.40-2.51 (1H, m), 2.66 (2H, q, J=7.2Hz), 2.82-2.88 (2H, m), 3.50 (2H, s), 7.20-7.33 (5H, m).

Reference Example 72

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-(4-methylpiperazin-1-yl)phenyl borate (0.44g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.07g), and the mixture was refluxed

over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give colorless crystals (0.39g), which were dissolved in 1N sodium hydroxide (15ml) and methanol (100ml). The mixture was refluxed for 2 hours, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-(4-methylpiperazin-1-yl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.33g) as colorless crystals.

mp 278-279°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 2.24 (3H, s), 2.45-2.52 (4H, m), 2.87 (2H, t, J=4.0Hz), 3.15-3.20 (4H, m), 4.23 (2H, t, J=4.8Hz), 6.97-7.01 (3H, m), 7.49-7.62 (4H, m), 7.70 (1H, d, J=2.2Hz). IR(KBr) ν: 1692cm⁻¹.

Anal. for C₂₂H₂₄N₂O₃·0.5H₂O:

Calcd. C, 70.76; H, 6.75; N, 7.50.

Found C, 70.87; H, 6.50; N, 7.56.

Reference Example 73

In 1,2-dichloroethane (35ml) were suspended 4-methylcyclohexanone (2.5g), methylamine hydrochloride (1.6g) and triethylamine (3.3ml), and to the suspension was added sodium triacetoxy boron hydride (6.6g) under ice-cooling. The mixture was stirred under nitrogen atmosphere at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated. To the residue was added 4N hydrochloric acid-ethyl acetate, and the solvent was evaporated to give N,4-dimethyl-cyclohexylamine hydrochloride (2.6g) as colorless crystals.

¹H-NMR(δ ppm, CDCl₃): 0.90 (1.5H, d, J=6.6Hz), 1.01 (1.5H,

d, J=6.6Hz), 1.45-2.10 (8H, m), 2.19-2.26 (1H, m), 2.61-2.68 (3H, m), 3.03 (1H, br).

Anal. for $C_8H_{10}ClN$:

Calcd. C, 58.70; H, 11.08; N, 8.56.

5 Found C, 58.42; H, 10.91; N, 8.48.

Reference Example 74

In 1,2-dichloroethane (25ml) were suspended p-nitro-benzylamine hydrochloride (1.2g), tetrahydropyran-3-one (0.6g; Numata et al., JP-A-63-170372) and triethylamine
10 (0.9ml), and to the suspension was added sodium triacetoxy boron hydride (1.8g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (0.6ml) and sodium triacetoxy boron hydride (1.8g).
15 Under nitrogen atmosphere, the mixture was stirred at room temperature over night, and the solvent was evaporated. The residue was neutralized with sodium hydroxide, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced
20 pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow oil (1.0g), to which was added reduced iron (0.6g) and acetic acid (50ml). The mixture was stirred at
25 room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium
30 sulfate. Under reduced pressure, the solvent was evaporated to give 4-(N-methyl-N-(tetrahydropyran-3-yl)-aminomethyl)aniline (0.3g) as brown oil.
 $^1\text{H-NMR}$ (δ ppm, CDCl_3): 1.46-1.75 (3H, m), 1.95-2.01 (1H, m), 2.19 (3H, s), 2.55-2.68 (1H, m), 3.21-3.40 (2H, m), 3.49
35 (2H, s), 3.59 (2H, br), 3.83-3.89 (1H, m), 4.00-4.08 (1H, m), 6.64 (2H, d, J=8.4Hz), 7.07 (2H, d, J=8.4Hz).

IR(neat) ν : 2941, 2846, 1615 cm^{-1} .

Reference Example 75

In 1,2-dichloroethane (50ml) were suspended 2-amino-indane hydrochloride (1.0g), p-nitrobenzaldehyde (0.9g) and triethylamine (0.9ml), and to the mixture was added sodium triacetoxy boron hydride (1.8g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (0.6ml) and sodium triacetoxy boron hydride (1.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night, and the solvent was evaporated. The residue was neutralized with sodium hydroxide, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give colorless crystals (1.7g), which was dissolved in ethanol (50ml) and ethyl acetate (50ml). To the mixture was added 10% palladium on carbon (0.15g), and catalytic hydrogenation was carried out at room temperature for 1 hour. The catalyst was filtered off, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate) to give 4-((N-indan-2-yl-N-methyl)aminomethyl)aniline (0.6g) as colorless crystals. mp 95-96°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 2.17 (3H, s), 2.91-3.16 (4H, m), 3.32-3.43 (1H, m), 3.47 (2H, s), 3.61 (2H, br), 6.66 (2H, d, $J=8.8\text{Hz}$), 7.10-7.22 (6H, m).

IR(KBr) ν : 2782, 1623 cm^{-1} .

Anal. for $\text{C}_{17}\text{H}_{20}\text{N}_2 \cdot 0.2\text{H}_2\text{O}$:

Calcd. C, 79.77; H, 8.03; N, 10.94.

Found C, 79.87; H, 8.04; N, 10.75.

Reference Example 76

In 1,2-dichloroethane (50ml) were suspended p-nitrobenzylamine hydrochloride (1.9g), 4-t-butylcyclohexanone (1.5g) and triethylamine (1.4ml), and to the suspension was

- added sodium triacetoxy boron hydride (3g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (0.9ml) and sodium triacetoxy boron hydride (3g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night, and the solvent was evaporated. The residue was neutralized with sodium hydroxide, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give (E)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitro-benzyl)amine (0.3g) as colorless crystals and (Z)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitrobenzyl)amine (2.4g) as yellow oil. (E)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitrobenzyl)-amine :
- mp 96-97°C.
- ¹H-NMR(δ ppm, CDCl₃): 0.85 (9H, s), 0.94-1.05 (3H, m), 1.20-1.40 (2H, m), 1.80-2.00 (4H, m), 2.19 (3H, s), 2.29-2.44 (1H, m), 3.65 (2H, s), 7.51 (2H, d, J=8.4Hz), 8.17 (2H, d, J=8.4Hz).
- IR(KBr) ν: 2941, 1604, 1513cm⁻¹.
- Anal. for C₁₈H₂₈N₂O₂:
- Calcd. C, 71.02; H, 9.27; N, 9.20.
- Found C, 70.77; H, 9.26; N, 9.32.
- (Z)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitrobenzyl)-amine :
- ¹H-NMR(δ ppm, CDCl₃): 0.89 (9H, s), 1.15-1.20 (1H, m), 1.30-1.54 (6H, m), 1.97-2.10 (2H, m), 2.08 (3H, s), 2.38 (1H, br), 3.61 (2H, s), 7.52 (2H, d, J=8.4Hz), 8.18 (2H, d, J=8.4Hz).
- IR(neat) ν: 2943, 1606, 1521cm⁻¹.
- Reference Example 77
- In ethanol (25ml) and ethyl acetate (25ml) was

dissolved (E)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitrobenzyl)amine (0.3g). To the mixture was added 10% palladium on carbon (0.03g) and catalytic hydrogenation was carried out at room temperature for 1 hour. The catalyst
5 was filtered off, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give (E)-4-((N-4-t-butylcyclohexyl-N-methyl)aminomethyl)aniline (0.2g) as colorless crystals.

10 mp 87-88°C.

¹H-NMR(δ ppm, CDCl₃): 0.84 (9H, s), 0.93-1.03 (2H, m), 1.15-1.40 (2H, m), 1.81-1.96 (5H, m), 2.19 (3H, s), 2.30-2.45 (1H, m), 3.48 (2H, s), 3.60 (2H, br), 6.65 (2H, d, J=8.4Hz), 7.10 (2H, d, J=8.4Hz).

15 IR(KBr) ν: 2927, 1614, 1517cm⁻¹.

Anal. for C₁₈H₂₆N₂·0.2H₂O:

Calcd. C, 77.75; H, 11.02; N, 10.07.

Found C, 77.87; H, 10.93; N, 10.16.

Reference Example 78

20 In acetic acid (70ml) was dissolved (Z)-N-(4-t-butylcyclohexyl)-N-methyl-N-(4-nitrobenzyl)amine (1.2g), and to the mixture was added reduced iron (1.1g). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The
25 precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel
30 column (ethyl acetate to give (Z)-4-((N-4-t-butylcyclohexyl-N-methyl)aminomethyl)aniline (0.7g) as yellow oil.

¹H-NMR(δ ppm, CDCl₃): 0.87 (9H, s), 1.00-1.20 (1H, m), 1.25-1.56 (6H, m), 2.04 (3H, s), 2.04-2.13 (2H, m), 2.26-2.29
35 (1H, m), 3.40 (2H, s), 3.58 (2H, br), 6.65 (2H, d, J=8.4Hz), 7.10 (2H, d, J=8.4Hz).

IR(neat) ν : 2941, 1623, 1515 cm^{-1} .

Reference Example 79

In 1,2-dichloroethane (70ml) were suspended p-nitro-benzylamine hydrochloride (3.8g), 3,5-dimethylcyclo-
5 hexanone (2.5g) and triethylamine (2.8ml). Under ice-cooling, to the mixture was added sodium triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin(1.8ml) and sodium
10 triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and
15 saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give 3 isomers of N-methyl-N-(3,5-dimethylcyclohexyl)-N-(4-nitrobenzyl)-
20 amine (4.3g; (31-a), 0.7g; (31-b), 0.2g; (31-c)) as each yellow oil.

31-a: $^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.53-0.74 (1H, m), 0.84 (3H, s), 0.87 (3H, s), 0.93-1.07 (2H, m), 1.73-1.99 (5H, m), 2.06 (3H, s), 2.49 (1H, t, $J=2.8\text{Hz}$), 3.60 (2H, s), 7.50 (2H, d, $J=8.8\text{Hz}$), 8.17 (2H, d, $J=8.8\text{Hz}$).

IR(neat) ν : 2949, 1606, 1521 cm^{-1} .

31-b: $^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.51 (1H, q, $J=12.0\text{Hz}$), 0.80-1.02 (2H, m), 0.92 (3H, s), 0.95 (3H, s), 1.34-1.53 (2H, m), 1.58-1.66 (1H, m), 1.78-1.84 (2H, m), 2.19 (3H, s), 2.53
30 (1H, tt, $J=3.3, 11.7\text{Hz}$), 3.65 (2H, s), 7.51 (2H, d, $J=8.8\text{Hz}$), 8.17 (2H, d, $J=8.8\text{Hz}$).

IR(neat) ν : 2949, 1606, 1519 cm^{-1} .

31-c: $^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.80-1.13 (8H, m), 1.38-1.52 (2H, m), 1.62-1.68 (2H, m), 1.80-1.86 (1H, m), 2.08-2.17 (1H, m), 2.18 (3H, s), 2.74 (1H, tt, $J=3.5, 11.9\text{Hz}$), 3.64 (2H, s), 7.51 (2H, d, $J=8.4\text{Hz}$), 8.17 (2H, d, $J=8.4\text{Hz}$).

IR(neat) ν : 2920, 1606, 1521 cm^{-1} .

Reference Example 80

In ethanol (50ml) and ethyl acetate (50ml) was dissolved N-methyl-N-(3,5-dimethylcyclohexyl)-N-(4-nitrobenzyl)amine (2.0g; (31-a)). To the mixture was added 10% palladium on carbon (0.2g) and catalytic hydrogenation was carried out at room temperature for 1 hour. The catalyst was filtered off, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)aminomethyl)aniline (0.2g) as pale yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.58 (1H, q, $J=11.7\text{Hz}$), 0.83 (3H, s), 0.86 (3H, s), 0.93-1.00 (2H, m), 1.69-2.04 (5H, m), 2.04 (3H, s), 2.24-2.40 (1H, m), 3.41 (2H, s), 3.50 (2H, br), 6.64 (2H, d, $J=8.6\text{Hz}$), 7.08 (2H, d, $J=8.6\text{Hz}$).

IR(neat) ν : 2947, 1623 cm^{-1} .

Reference Example 81

In acetic acid (30ml) was dissolved N-methyl-N-(3,5-dimethylcyclohexyl)-N-(4-nitrobenzyl)amine (0.7g; (31-b)), and to the mixture was added reduced iron (0.7g). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)aminomethyl)aniline (0.4g) as yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.50 (1H, q, $J=12.0\text{Hz}$), 0.80-1.03 (1H, m), 0.91 (3H, s), 0.94 (3H, s), 1.22-1.50 (3H, m), 1.55-1.64 (1H, m), 1.78-1.84 (2H, m), 2.17 (3H, s), 2.53 (1H, tt, $J=3.3, 11.8\text{Hz}$), 3.46 (2H, s), 3.58 (2H, br), 6.64 (2H, d, $J=8.6\text{Hz}$), 7.09 (2H, d, $J=8.6\text{Hz}$).

IR(neat) ν : 2949, 1621 cm^{-1} .

Reference Example 82

In acetic acid (15ml) was dissolved N-methyl-N-(3,5-dimethylcyclohexyl)-N-(4-nitrobenzyl)amine (0.2g; (31-c)), and to the mixture was added reduced iron (0.2g). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-(3,5-dimethylcyclohexyl)-N-methyl)aminomethyl)aniline (0.1g) as brown oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3): 0.87-1.15 (7H, m), 1.35-1.55 (2H, m), 1.60-1.70 (2H, m), 1.75-1.90 (1H, m), 2.05-2.19 (2H, m), 2.17 (3H, s), 2.75 (1H, tt, $J=3.3, 12.1\text{Hz}$), 3.45 (2H, s), 3.60 (2H, br), 6.64 (2H, d, $J=8.3\text{Hz}$), 7.09 (2H, d, $J=8.3\text{Hz}$).

Reference Example 83

In 1,2-dichloroethane (50ml) were dissolved n-propylamine (1.1g) and p-nitrobenzaldehyde (2.3g). Under ice-cooling, to the mixture was added sodium triacetoxo boron hydride (4.5g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (1.7ml) and sodium triacetoxo boron hydride (4.5g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night, and the solvent was evaporated. The residue was neutralized with sodium hydroxide, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow oil (2.3g), which was dissolved in tetrahydrofuran (10ml). The mixture

was dropwise added to a solution, which was prepared by adding dropwise lithium aluminum hydride (0.5g) to a solution of titanium tetrachloride (2ml) in tetrahydrofuran (50ml), under ice-cooling, and stirring the mixture at room temperature for 15 minutes, under ice-cooling. The mixture was stirred at room temperature for 30 minutes, and to the mixture were added water (50ml) and ammonia solution (50ml). The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-methyl-N-n-propyl)aminomethyl)aniline (0.25g) as yellow oil.

¹H-NMR(δ ppm, CDCl₃): 0.88 (3H, t, J=7.3Hz), 1.43-1.61 (2H, m), 2.16 (3H, s), 2.30 (2H, t, J=7.7Hz), 3.37 (2H, s), 3.59 (2H, br), 6.64 (2H, d, J=8.0Hz), 7.08 (2H, d, J=8.0Hz). IR(neat) ν: 2960, 1623, 1517cm⁻¹.

Reference Example 84

In 1,2-dichloroethane (50ml) were dissolved isopropylamine (1g) and p-nitrobenzaldehyde (2.3g), and to the mixture was added sodium triacetoxy boron hydride (4.5g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (1.5ml) and sodium triacetoxy boron hydride (4.5g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give yellow oil (2.8g), 1.5g of which was dissolved in ethanol (25ml)

and ethyl acetate (25ml). To the mixture was added 10% palladium on carbon (0.15g), and catalytic hydrogenation was carried out at room temperature for 1 hour. The catalyst was filtered off, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-isopropyl-N-methyl)aminomethyl)aniline (0.17g) as pale yellow oil.

¹H-NMR (δ ppm, CDCl₃): 1.05 (6H, d, J=6.6Hz), 2.13 (3H, s), 2.81-2.95 (1H, m), 3.40 (2H, s), 3.60 (2H, br), 6.65 (2H, d, J=8.4Hz), 7.10 (2H, d, J=8.4Hz).
IR(neat) ν: 2966, 1623, 1517cm⁻¹.

Reference Example 85

In 1,2-dichloroethane (50ml) were dissolved 1-methyl-propylamine (1.3g) and p-nitrobenzaldehyde (2.3g), and to the mixture was added sodium triacetoxy boron hydride (4.5g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (1.7ml) and sodium triacetoxy boron hydride (4.5g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown oil (3.4g), 2.0g of which was dissolved in tetra-hydrofuran (20ml). The mixture was dropwise added to a solution, which was prepared by adding dropwise lithium-aluminum hydride (0.7g) to a solution of titanium tetrachloride (3ml) in tetrahydrofuran (50ml) under ice-cooling and stirring the mixture at room temperature for 15 minutes, under ice-cooling. The mixture was stirred at room temperature over night, and, to the mixture were added water (75ml) and ammonia solution (75ml). The mixture was extracted with ethyl acetate. The organic

layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/
5 methanol/triethylamine) to give 4-((N-sec-butyl-N-methyl)aminomethyl)aniline (0.8g) as yellow oil.
¹H-NMR(δ ppm, CDCl₃): 0.87-0.99 (6H, m), 1.22-1.37 (1H, m), 1.53-1.63 (1H, m), 2.11 (3H, s), 2.53-2.63 (1H, m), 3.34 (1H, d, J=12.8Hz), 3.46 (1H, d, J=12.8Hz), 3.57 (2H, br),
10 6.64 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).
IR(neat) ν: 2962, 2933, 2873, 1617, 1517cm⁻¹.
Reference Example 86

In 1,2-dichloroethane (70ml) were dissolved t-butylamine (1.6g) and p-nitrobenzaldehyde (3.0g), and to the
15 mixture was added sodium triacetoxy boron hydride (5.9g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (2ml) and sodium triacetoxy boron hydride (5.9g). Under nitrogen
20 atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried
25 with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, to give brown oil (4.4g), which was dissolved in acetic acid (50ml). To the mixture was added reduced iron (3.2g), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to
30 the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was
35 evaporated to give 4-((N-t-butyl-N-methyl)aminomethyl)aniline (2.2g) as brown oil.

¹H-NMR(δ ppm, CDCl₃): 1.14 (9H, s), 2.07 (3H, s), 3.38 (2H, s), 3.57 (2H, br), 6.64 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).

IR(neat) ν: 2971, 1622, 1516cm⁻¹.

5 Reference Example 87

In 1,2-dichloroethane (70ml) were suspended p-nitrobenzylamine hydrochloride (3.8g) and 3-pentanone (1.7g), and to the suspension was added triethylamine (2.8ml). Under ice-cooling, to the mixture was added sodium triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (1.8ml) and sodium triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give pale yellow oil (4.6g), which was dissolved in acetic acid (100ml). To the mixture was added reduced iron (4.7g), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-((N-methyl-N-(pentan-3-yl))-amino-methyl)aniline (3.3g) as pale brown oil.

¹H-NMR(δ ppm, CDCl₃): 0.92 (6H, t, J=7.3Hz), 1.20-1.59 (4H, m), 2.10 (3H, s), 2.18-2.29 (1H, m), 3.44 (2H, s), 3.57 (2H, br), 6.64 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.4Hz).

IR(neat) ν: 2959, 1622, 1516cm⁻¹.

35 Reference Example 88

In 1,2-dichloroethane (70ml) were suspended p-nitro-

benzylamine hydrochloride (3.8g) and norcamphor (2.2g), and to the suspension was added triethylamine (2.8ml). Under ice-cooling, to the mixture was added sodium triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. Under ice-cooling, to the mixture were added 37% formalin (1.8ml) and sodium triacetoxy boron hydride (5.9g). Under nitrogen atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give pale yellow oil (5.2g), which was dissolved in acetic acid (100ml). To the mixture was added reduced iron (5g), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-((N-methyl-N-(norbornan-2-yl))amino-methyl)aniline (4.0g) as pale brown oil.

¹H-NMR(δ ppm, CDCl₃): 0.94-1.04 (1H, m), 1.22-1.55 (5H, m), 1.68-1.97 (2H, m), 2.00 (3H, s), 2.16 (1H, br), 2.37 (2H, br), 3.22 (1H, d, J=12.8Hz), 3.42 (1H, d, J=12.8Hz), 3.58 (2H, br), 6.64 (2H, d, J=8.4Hz), 7.09 (2H, d, J=8.4Hz). IR(neat) ν: 2949, 1622, 1516cm⁻¹.

30 Reference Example 89

To a mixture of p-nitrophenethylbromide (2.3g), N-methylcyclohexylamine (2.8g), potassium carbonate (6.6g) and sodium iodide (1.5g) was added dimethylformamide (50ml), and the mixture was stirred at 50°C over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer

was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/
5 methanol/triethylamine) to give yellow oil (2.2g), which was dissolved in ethanol (50ml). To the mixture was added 10% palladium on carbon (0.2g), and catalytic hydrogenation was carried out at room temperature over night. The catalyst was filtered off, and the solvent was evaporated
10 to give 4-(2-(N-cyclohexyl-N-methyl)aminoethyl)aniline (1.9g) as pale yellow oil.
¹H-NMR(δ ppm, CDCl₃): 1.05-1.30 (6H, m), 1.60-1.79 (4H, m), 2.33 (3H, s), 2.33-2.45 (1H, m), 2.61-2.63 (4H, m), 3.55 (2H, br), 6.63 (2H, d, J=8.4Hz), 6.99 (2H, d, J=8.4Hz).
15 IR(neat) ν: 2929, 1625, 1517cm⁻¹.

Reference Example 90

In ethanol (15ml) were dissolved p-nitrostyreneoxide (0.5g; E. Borredon et al., J. Org. Che., 1990, 55, 501-504) and piperidine (0.36ml), and the mixture was refluxed
20 for 1 hour. The solvent was evaporated to give yellow crystals (0.53g), which was dissolved in ethanol (50ml). To the mixture was added 5% palladium on carbon (0.05g), and catalytic hydrogenation was carried out at room temperature 1.5 hours. The catalyst was filtered off, and
25 the solvent was evaporated, 4-(1-hydroxy-2-piperidino-ethyl)aniline (0.4g) as colorless crystals.
mp 75-76°C.

¹H-NMR(δ ppm, CDCl₃): 1.40-1.50 (2H, m), 1.55-1.70 (4H, m), 2.31-2.41 (4H, m), 2.62-2.75 (2H, m), 3.61 (2H, br), 4.61
30 (1H, dd, J=6.2, 8.0Hz), 6.66 (2H, d, J=8.4Hz), 7.15 (2H, d, J=8.4Hz).

IR(KBr) ν: 2936, 1622, 1518cm⁻¹.

Anal. for C₁₃H₂₀N₂O:

Calcd. C, 70.87; H, 9.15; N, 12.72.

35 Found C, 71.02; H, 9.10; N, 13.01.

Reference Example 91

In dimethylformamide (50ml) were dissolved methyl 5-bromosalicylate (5g), ethyl 4-bromobutyrate (4.2g) and potassium carbonate (7.5g), and the mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless oil (6.5g), which was dissolved in tetrahydrofuran (20ml). The mixture was dropwise added to a solution of lithium diisopropylamine in tetrahydrofuran prepared by diisopropylamine (3.2ml) and n-butyllithium in hexane (1.6M, 13ml), at -78°C. The mixture was stirred at room temperature under argon atmosphere over night and poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give oil, which was dissolved in dichloromethane (100ml). The mixture was dropwise added to a solution of sodium boron hydride in methanol at -15°C. After starting materials disappeared, water was added to the reaction mixture, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was dissolved in dichloromethane (100ml). To the mixture was added triethylamine (7.9ml), and to the mixture was dropwise added methanesulfonylchloride (2.2ml) under ice-cooling. The mixture was stirred at room temperature under nitrogen atmosphere over night, and to the mixture was added water. The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and

dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (2.3g) as colorless crystals.

mp 86-87°C.

¹H-NMR (δ ppm, CDCl₃): 1.35 (3H, t, J=7.2Hz), 2.98 (2H, t, J=4.7Hz), 4.23-4.33 (4H, m), 6.86 (1H, d, J=8.8Hz), 7.32 (1H, dd, J=2.6, 8.8Hz), 7.46-7.47 (2H, m).

10 Reference Example 92

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), diethyl(3-pyridyl)-borane (0.26g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)-phosphinepalladium (0.07g), and the mixture was refluxed over night. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.28g), which were dissolved in 1N sodium hydroxide (10ml) and methanol (50ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(3-pyridyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.3g) as colorless crystals.

mp >300°C.

30 ¹H-NMR (δ ppm, DMSO-d₆): 2.89 (2H, t, J=4.6Hz), 4.27 (2H, t, J=4.6Hz), 7.09 (1H, d, J=8.4Hz), 7.46 (1H, dd, J=4.6, 7.8Hz), 7.64-7.69 (2H, m), 7.90 (1H, d, J=2.2Hz), 8.10 (1H, dt, J=7.8, 1.5Hz), 8.54 (1H, dd, J=1.5, 4.6Hz), 8.92 (1H, d, J=2.2Hz). IR(KBr) ν: 1699cm⁻¹.

35 Anal. for C₁₆H₁₃NO·0.2H₂O:

Calcd. C, 70.94; H, 4.99; N, 5.17.

Found C, 70.71; H, 5.00; N, 5.17.

Reference Example 93

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (1.0g), 4-pyridyl borate (0.46g),
5 1M potassium carbonate (11ml) and ethanol (11ml) was added toluene (80ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.16g), and the mixture was refluxed over night and extracted with ethyl
10 acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless oil (0.52g),
15 which was dissolved in 1N sodium hydroxide (18ml) and methanol (100ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-pyridyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.34g) as
20 colorless crystals.
mp 277-278°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 2.89 (2H, t, J=4.8Hz), 4.28 (2H, t, J=4.8Hz), 7.10 (1H, d, J=8.6Hz), 7.68 (1H, s), 7.74-7.79 (3H, m), 8.02 (1H, d, J=2.2Hz), 8.61 (2H, d, J=5.6Hz).

25 Anal. for C₁₆H₁₃NO₃·0.1H₂O:

Calcd. C, 71.42; H, 4.94; N, 5.21.

Found C, 71.30; H, 4.80; N, 5.05.

Reference Example 94

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 2-furyl borate (0.22g),
30 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml) and, the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium
35 (0.07g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed

with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give
5 colorless crystals (0.37g), which were dissolved in 1N sodium hydroxide (10ml) and methanol (50ml). The mixture was stirred at room temperature over night, concentrated and acidified with hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed
10 with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-(2-furyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.3g) as colorless crystals.

15 mp 234-235°C(dec.).

¹H-NMR(δ ppm, CDCl₃): 3.02 (2H, t, J=4.7Hz), 4.32 (2H, t, J=4.7Hz), 6.47 (1H, dd, J=1.5, 3.2Hz), 6.58 (1H, dd, J=0.7, 3.2Hz), 7.02 (1H, d, J=8.6Hz), 7.46 (1H, dd, J=0.7, 1.5Hz), 7.57 (1H, dd, J=2.2, 8.6Hz), 7.68 (1H, d, J=2.2Hz), 7.77
20 (1H, s).

IR(KBr) ν: 1686cm⁻¹.

Anal. for C₁₅H₁₂O₄:

Calcd. C, 70.31; H, 4.72.

Found C, 70.31; H, 4.73.

25 Reference Example 95

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-dimethylaminophenyl borate (0.3g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred
30 under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.07g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution,
35 and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was

purified with silica gel column (ethyl acetate/hexane) to give pale yellow crystals (0.45g), which were dissolved in 1N sodium hydroxide (15ml), methanol (100ml) and tetrahydrofuran (25ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-dimethylamino-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.4g) as pale yellow crystals.

mp 281-282°C (dec.).

¹H-NMR (δ ppm, DMSO-d₆): 2.87 (2H, t, J=4.6Hz), 2.93 (6H, s), 4.23 (2H, t, J=4.6Hz), 6.78 (2H, d, J=8.8Hz), 6.99 (1H, d, J=8.4Hz), 7.47-7.54 (3H, m), 7.62 (1H, s), 7.67 (1H, d, J=2.2Hz).

IR(KBr) ν: 1676cm⁻¹.

Anal. for C₁₉H₁₉NO₃:

Calcd. C, 73.77; H, 6.19; N, 4.53.

Found C, 73.57; H, 6.22; N, 4.64.

Reference Example 96

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-(pyrrolidin-1-yl)phenyl borate (0.35g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.07g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give pale yellow crystals (0.55g), which were dissolved in 1N sodium hydroxide (15ml), methanol (25ml) and tetrahydrofuran (25ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-(pyrrolidin-1-yl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid

(0.5g) as pale yellow crystals.

mp 266-267°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 1.94-2.00 (4H, m), 2.87 (2H, t, J=4.4Hz), 3.25-3.30 (4H, m), 4.22 (2H, t, J=4.4Hz), 6.59 (2H, d, J=8.8Hz), 6.98 (1H, d, J=8.4Hz), 7.45-7.52 (3H, m), 7.61 (1H, s), 7.65 (1H, d, J=2.2Hz).

IR(KBr) ν: 1678cm⁻¹.

Anal. for C₂₁H₂₁NO₃·0.2H₂O:

Calcd. C,74.40; H,6.36; N,4.13.

10 Found C,74.49; H,6.39; N,4.47.

Reference Example 97

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-piperidinophenyl borate (0.38g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.07g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.62g), which were dissolved in 1N sodium hydroxide (10ml), methanol (25ml) and tetrahydrofuran (25ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-piperidino-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.6g) as pale yellow crystals.

mp 262-263°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 1.50-1.75 (6H, m), 2.87 (2H, t, J=4.8Hz), 3.15-3.19 (4H, m), 4.23 (2H, t, J=4.8Hz), 6.96 (2H, d, J=8.8Hz), 7.00 (1H, d, J=8.4Hz), 7.51 (1H, dd, J=2.4, 8.4Hz), 7.52 (2H, d, J=8.8Hz), 7.62 (1H, s), 7.68 (1H, d, J=2.4Hz).

IR(KBr) ν : 2932, 1690 cm^{-1} .

Reference Example 98

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-morpholinophenyl borate (0.39g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphine-palladium (0.07g), and the mixture was refluxed for 4 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.54g), which were dissolved in 1N sodium hydroxide (15ml), methanol (100ml) and tetrahydrofuran (100ml). The mixture was stirred at room temperature over night, concentrated and neutralized with hydrochloric acid to precipitate 7-(4-morpholino-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.44g) as colorless crystals.

mp 291-292°C(dec.).

$^1\text{H-NMR}$ (δ ppm, DMSO- d_6): 2.87 (2H, t, $J=4.8\text{Hz}$), 3.12-3.17 (4H, m), 3.73-3.78 (4H, m), 4.23 (2H, t, $J=4.8\text{Hz}$), 7.00 (3H, d, $J=8.4\text{Hz}$), 7.51 (1H, dd, $J=2.4, 8.4\text{Hz}$), 7.56 (2H, d, $J=8.8\text{Hz}$), 7.60 (1H, s), 7.69 (1H, d, $J=2.4\text{Hz}$).

Anal. for $\text{C}_{21}\text{H}_{21}\text{NO}_4$:

Calcd. C, 71.78; H, 6.02; N, 3.99.

Found C, 71.42; H, 6.19; N, 4.16.

Reference Example 99

To a mixture of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.5g), 4-(1-imidazolyl)phenyl borate (0.38g), 1M potassium carbonate (7ml) and ethanol (7ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphine-

palladium (0.07g), and the mixture was refluxed for 4 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced
5 pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give colorless crystals (0.53g), which were dissolved in 1N sodium hydroxide (10ml) and methanol (50ml). The mixture was stirred at room temperature over night, concentrated
10 and neutralized with hydrochloric acid to precipitate 7-(4-(1-imidazolyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.44g) as colorless crystals.
mp >300°C.

¹H-NMR (δ ppm, DMSO-d₆): 2.89 (2H, t, J=4.5Hz), 4.26 (2H, t, J=4.5Hz), 7.07 (1H, d, J=8.4Hz), 7.13 (1H, s), 7.55-7.68 (3H, m), 7.73 (2H, d, J=8.8Hz), 7.81 (1H, s), 7.85 (2H, d, J=8.8Hz), 8.33 (1H, s).

Anal. for C₂₀H₁₆N₂O₃·0.3H₂O:

Calcd. C, 71.12; H, 4.95; N, 8.29.

20 Found C, 71.15; H, 4.84; N, 8.21.

Reference Example 100

In 1,2-dichloroethane (100ml) was suspended p-nitrobenzylamine hydrochloride (8.1g), 4H-tetrahydrothiopyran-4-one (5.0g) and triethylamine (6ml), and to the
25 suspension was added sodium triacetoxo boron hydride (12.8g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature for 9 hours. Under ice-cooling, to the mixture were added 37% formalin (3.9ml) and sodium triacetoxo boron hydride (12.8g). Under nitrogen
30 atmosphere, the mixture was stirred at room temperature over night. The solvent was evaporated, and the residue was neutralized with sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried
35 with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow oil (11.5g), to

which were added reduced iron (12g) and acetic acid (200ml). The mixture was stirred at room temperature over night. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate
5 was washed with sodium hydrogen carbonate solution, water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine)
10 to give 4-(N-methyl-N-(tetrahydrothiopyran-4-yl)amino-methyl)aniline (8.8g) as pale yellow crystals.
mp 88-89°C.

¹H-NMR (δ ppm, CDCl₃): 1.65-1.84 (2H, m), 2.10-2.18 (2H, m),
2.19 (3H, s), 2.45 (1H, tt, J=3.2, 13.0Hz), 2.65-2.71 (4H,
15 m), 3.47 (2H, s), 3.61 (2H, br), 6.64 (2H, d, J=8.4Hz), 7.08
(2H, d, J=8.4Hz).

IR(KBr) ν : 2932, 1620cm⁻¹.

Anal. for C₁₃H₂₀N₂S:

Calcd. C, 66.06; H, 8.53; N, 11.85.

20 Found C, 66.03; H, 8.35; N, 11.78.

Reference Example 101

A mixture of sodium methoxide (12.5g) and dimethyl carbonate (150ml) was added to 3-bromo-6,7,8,9-tetra-
hydro-5H-benzocycloheptan-5-one (10.8g), and the mixture
25 was refluxed for 8 hours under nitrogen atmosphere. Under ice-cooling, the mixture was poured into 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The
30 solvent was evaporated to give brown oil (13.1g), which was dissolved in dichloromethane (150ml). To the mixture was dropwise added sodium boron hydride dissolved in methanol, under ice-cooling. After starting materials disappeared, water was added to the reaction mixture, and the mixture
35 was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride

- solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was dissolved in dichloromethane (150ml). To the mixture was added triethylamine (29ml), and to the mixture was dropwise added methane-sulfonylchloride (5.3ml) under ice-cooling. The mixture was stirred at room temperature under nitrogen atmosphere over night, and to the mixture was added water. The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give methyl 2-bromo-6,7-dihydro-5H-benzo-cycloheptene-8-carboxylate (1.7g) as colorless crystals.
- mp 83-84°C.
- ¹H-NMR(δ ppm, CDCl₃): 1.97-2.10 (2H, m), 2.62 (2H, t, J=6.6Hz), 2.72-2.78 (2H, m), 3.82 (3H, s), 7.02 (1H, d, J=8.0Hz), 7.32 (1H, dd, J=2.2, 8.0Hz), 7.45 (1H, d, J=2.2Hz), 7.60 (1H, s).
- IR(KBr) ν: 2946, 1713cm⁻¹.
- Anal. for C₁₃H₁₃BrO₂:
Calcd. C, 55.54; H, 4.66.
Found C, 55.56; H, 4.75.
- Reference Example 102
- To a mixture of methyl 2-bromo-6,7-dihydro-5H-benzo-cycloheptene-8-carboxylate (0.5g), 4-piperidinophenyl borate (0.4g), 1M potassium carbonate (6ml) and ethanol (6ml) was added toluene (50ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes.
- To the mixture was added tetrakis(triphenylphosphine)palladium (0.08g), and the mixture was refluxed over night and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate.
- Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/

hexane) to give colorless crystals (0.45g), which were dissolved in 1N sodium hydroxide (15ml), methanol (50ml) and tetrahydrofuran (50ml). The mixture was refluxed at room temperature for 2 hours, concentrated and neutralized with hydrochloric acid to precipitate 2-(4-piperidino-phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.46g) as colorless crystals.
mp 219-220°C(dec.).

¹H-NMR(δ ppm, DMSO-d₆): 1.50-1.70 (6H, m), 1.85-2.05 (2H, m), 2.56 (2H, t, J=6.4Hz), 2.80-2.82 (2H, s), 3.13-3.25 (4H, m), 6.99 (2H, d, J=8.7Hz), 7.23 (1H, d, J=8.0Hz), 7.47 (1H, dd, J=1.8, 8.0Hz), 7.54 (2H, d, J=8.7Hz), 7.60 (1H, d, J=1.8Hz), 7.70 (1H, s).

Anal. for C₂₃H₂₅NO₂·0.2H₂O:

Calcd. C, 78.69; H, 7.29; N, 3.99.

Found C, 78.82; H, 7.38; N, 3.89.

Reference Example 103

To a mixture of N-t-butoxycarbonylpiperidin-4-one (3g; M. S. Ashwood et al., J. Chem. Soc. Perkin Trans. 1, 1995, 641-644) and methylamine hydrochloride (1g) were added triethylamine (2.1ml) and 1,2-dichloroethane(50ml). Under ice-cooling, to the mixture was added sodium triacetoxyl boron hydride (4.5g), and the mixture was stirred under nitrogen atmosphere at room temperature for 4 hours. The mixture was neutralized with sodium hydroxide, concentrated and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 1-t-butoxy-carbonyl-4-methylaminopiperidine (3.1g) as colorless oil.

¹H-NMR(δ ppm, CDCl₃): 1.13-1.33 (3H, m), 1.33-1.54 (3H, m), 1.45 (9H, s), 1.83-1.88 (2H, m), 2.44 (3H, s), 2.44-2.56 (1H, m), 2.73-2.87 (2H, m), 4.01 (1H, br).

Reference Example 104

In chlorobenzene (100ml) was dissolved 2-bromo-4'-acetophenone (25.1g), and the mixture was dropwise added

to a suspension of hexamethylenetetramine (15.9g) in chlorobenzene (100ml). The mixture was stirred under nitrogen atmosphere at 60°C for 4 hours and cooled to precipitate crystals, which were filtered and washed with ethanol and diethylether. The resulting crystals were added little by little to a mixture of 95% ethanol (100ml) and hydrochloric acid (50ml), and the mixture was stirred at room temperature over night. Precipitated crystal was filtered and washed with diethylether. To the crystal was added di-t-butyl bicarbonate (32g), triethylamine (29ml) and dichloromethane (500ml), and the mixture was stirred at room temperature for 2 hours, washed with water, 10% citric acid and water, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give yellow solid (24.9g), 12g of which was dissolved in ethanol (200ml) and ethyl acetate (50ml). To the mixture was added 10% palladium on carbon (1.2g) and catalytic hydrogenation was carried out at room temperature for 6 hours. The catalyst was filtered off, and the solvent was evaporated to give colorless crystals (6.5g), 4g of which was dissolved in dimethylformamide (50ml). To the mixture was added sodium hydride (60%, 1.4g) at -3°C, and the mixture was stirred for 20 minutes. To the mixture was dropwise added 1,4-dibromobutane (2.1ml), and the mixture was stirred under ice-cooling for 1.5 hours. To the mixture was ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, (4-aminophenyl)[1-(tert-butoxycarbonyl)piperidin-2-yl]methanone (2.1g) as pale yellow crystals.

mp 187-188°C.

¹H-NMR (δ ppm, CDCl₃): 1.42 (9H, br), 1.43 (2H, br), 1.80 (1H, br), 2.05 (1H, br), 3.22 (1H, br), 3.95 (1H, br), 4.09 (2H,

br), 5.55 (1H, br), 6.63 (2H, d, $J=8.4\text{Hz}$), 7.79 (2H, d, $J=8.4\text{Hz}$).

IR(KBr) ν : 3362, 2942, 1682 cm^{-1} .

Anal. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3 \cdot 0.1\text{H}_2\text{O}$:

5 Calcd. C, 66.69; H, 7.97; N, 9.15.

Found C, 66.60; H, 7.91; N, 8.87.

Reference Example 105

A mixture of 2-(4-nitrobenzyl)pyridine (J. Chem. Soc., p549, 1929) (1.50g) and 5% Pd-C (0.15g) in ethanol (30ml)
10 was vigorously stirred under hydrogen atmosphere for 8 hours, and the Pd-C was filtered off. The filtrate was concentrated under reduced pressure, and the residue was separated and purified with column chromatography (ethyl acetate/hexane=1:1→2:1) to give 2-(4-aminobenzyl)-
15 pyridine (1.09g) as yellow oil.

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 3.41-3.75 (2H, m), 4.05 (2H, s), 6.50-6.69 (2H, m), 6.97-7.16 (4H, m), 7.51-7.60 (1H, m), 8.48-8.57 (1H, m).

IR (neat) 3338, 3213, 3008, 1622, 1593, 1516, 1471, 1433,
20 1281, 754 cm^{-1}

Reference Example 106

Under nitrogen atmosphere, to a solution of ethyl magnesium chloride in tetrahydrofuran (1.58M, 95ml) was added diethyl phosphite (6.91g) under ice-cooling, and the
25 mixture was stirred at room temperature for 1 hour. To the mixture was added benzyl bromide (7.2ml), and the mixture was refluxed for 4 hours. The reaction mixture was vigorously stirred and concentrated hydrochloric acid-ice was added to the mixture to stop the reaction. The mixture was
30 extracted with diethylether and concentrated. To the residue was added chloroform, and the mixture was washed with water and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/ethanol=3:1→2:1) to give
35 benzyldiethylphosphine oxide (1.45g) as colorless crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.17 (6H, dt, J=16.6, 8.0 Hz), 1.57-1.75 (4H, m), 3.14 (2H, d, J=14.4 Hz), 7.19-7.40 (4H, m).

IR (KBr) 3396, 2974, 16445, 1495, 1458, 1410, 1242, 1159, 1124, 1034, 829, 789, 702 cm⁻¹

Reference Example 107

To a mixture of nitric acid (0.4ml) and concentrated sulfuric acid (3ml) was added benzyldiethylphosphine oxide (1.05g) at 0°C, and the mixture was stirred at 50°C for 1 hour. The reaction mixture was added to ice-water, and ammonia solution was added to the solution to neutralize the solution, which was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/ethanol=3:2→1:1) to give 4-nitrobenzyldiethylphosphine oxide (518mg) as pale yellow crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.18 (6H, dt, J=17.0, 8.0 Hz), 1.64-1.86 (4H, m), 3.23 (2H, d, J=13.6 Hz), 7.49 (2H, dd, J=8.8, 1.6 Hz), 8.20 (2H, d, J=8.8 Hz).

IR (KBr) 1599, 1506, 1340, 1169, 864, 773, 694, 501 cm⁻¹

Reference Example 108

A mixture of 4-nitrobenzyldiethylphosphine oxide (0.4g) and 10% Pd-C (0.06g) in ethanol (10ml) was vigorously stirred under hydrogen atmosphere for 16 hours, and the Pd-C was filtered off. The filtrate was concentrated under reduced pressure to give 4-aminobenzyldiethylphosphine oxide (349mg) as brown oil.

¹H-NMR (200MHz, CDCl₃) δ 1.16 (6H, dt, J=16.6, 7.8 Hz), 1.56-1.76 (4H, m), 3.02 (2H, d, J=14.4 Hz), 6.64 (2H, d, J=8.4 Hz), 7.03 (2H, dd, J=8.4, 1.8 Hz).

IR (neat) 3336, 1630, 1614, 1516, 1460, 1408, 1284, 1157, 1126, 841, 791, 768, 540 cm⁻¹

Reference Example 109

Under nitrogen atmosphere, to a solution of propyl

magnesium bromide in tetrahydrofuran (2M, 250g) was added diethyl phosphite (18.0g) under ice-cooling, and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added benzyl bromide (24.7ml), and the mixture was refluxed for 5 hours. The reaction mixture was vigorously stirred and added to concentrated hydrochloric acid-ice to stop the reaction. The mixture was extracted with ethyl acetate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate→ethyl acetate/ethanol=3:1) to give benzyldipropylphosphine oxide (25.33g) as colorless crystals.

¹H-NMR (200MHz, CDCl₃) δ 0.94-1.09 (6H, m), 1.49-1.75 (8H, m), 3.15 (2H, d, J=14.6 Hz), 7.19-7.39 (5H, m).
IR (KBr) 3425, 2964, 1645, 1603, 1497, 1456, 1242, 1161, 1126, 1080, 1030, 843 cm⁻¹

Reference Example 110

To a mixture of nitric acid (3.6ml) and concentrated sulfuric acid (22ml) was added benzyldipropylphosphine-oxide (10.75g) at 0°C, and the mixture was stirred at 60°C for 1.5 hours. The reaction mixture was added to ice-water, and ammonia solution was added to the mixture to neutralize the solution, which was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/ethanol=9:1→4:1) to give 4-nitrobenzyldipropylphosphine oxide (3.77g) as pale yellow crystals.

¹H-NMR (200MHz, CDCl₃) δ 0.96-1.09 (6H, m), 1.51-1.75 (8H, m), 3.20 (2H, d, J=13.6 Hz), 7.47 (2H, dd, J=8.8, 2.0 Hz), 8.21 (2H, d, J=8.8 Hz).

IR (KBr) 1527, 1431, 1352, 1028 cm⁻¹

Reference Example 111

A mixture of 4-nitrobenzyldipropylphosphine oxide (3.0g) and 5% Pd-C (0.3g) in ethanol (50ml) was vigorously

stirred under hydrogen atmosphere for 16 hours, and the Pd-C was filtered off. The filtrate was concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:5→
5 1:4) and recrystallized from ethanol-ethyl acetate to give 4-aminobenzylidipropylphosphine oxide (1.78g) as colorless crystals.

m.p. 104-106°C

¹H-NMR (200MHz, CDCl₃) δ 0.88-1.12 (6H, m), 1.43-1.72 (8H, m), 3.01 (2H, d, J=14.8 Hz), 3.52-3.76 (2H, m), 6.65 (2H, d, J=8.6 Hz), 7.01 (2H, dd, J=8.6, 2.0 Hz).

IR (KBr) 3348, 3209, 2058, 1608, 1512, 1155, 1126, 852 cm⁻¹

Elemental Analysis for C₁₃H₂₂NOP

Calcd. C, 65.25 ; H, 9.27 ; N, 5.85 ; P, 12.94 :

15 Found. C, 65.16 ; H, 9.04 ; N, 5.91 ; P, 12.94.

Reference Example 112

Under nitrogen atmosphere, to a solution of 2-bromo-3-hydroxypyridine (10.00g) in DMF (100ml) was added sodium hydride (60% oil, 2.5g) at 0°C, and the mixture was stirred
20 for 30 minutes. To the reaction mixture was added methyl iodide (4.0ml), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride
25 solution, dried with magnesium sulfate and concentrated. Under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate/hexane=1:2) to give 2-bromo-3-methoxypyridine (9.24g) as colorless crystals.

30 m.p. 41-43°C

¹H-NMR (200MHz, CDCl₃) δ 3.92 (3H, s), 7.15 (1H, dd, J=8.0, 1.4 Hz), 7.24 (1H, dd, J=8.0, 4.4 Hz), 7.99 (1H, dd, J=4.4, 1.4 Hz).

IR (KBr) 3055, 1562, 1468, 1414, 1298, 1205, 1078, 1049,
35 791, 667 cm⁻¹

Elemental Analysis for C₆H₆NO

Calcd. C, 38.33 ; H, 3.22 ; N, 7.45 :

Found. C, 38.35 ; H, 3.07 ; N, 7.28.

Reference Example 113

To a solution of 2-bromo-3-methoxypyridine (1.00g) in
5 diethylether (20ml) was added a solution of n-butyllithium
in hexane (1.6M, 3.7ml) at -78°C, and the mixture was stirred
for 1 hour to prepare the lithium salt, which was dropwise
added to a solution of 4-nitrobenzaldehyde (0.81g) in
10 tetrahydrofuran (10ml) cooled at -78°C. The mixture was
stirred at -78°C. To the reaction mixture was added water
to stop the reaction, and the mixture was extracted with
ethyl acetate. The organic layer was washed with saturated
sodium chloride solution, dried with magnesium sulfate and
concentrated. Under reduced pressure, the residue was
15 separated and purified with column chromatography (ethyl
acetate/hexane=1:3→1:1) to give 3-methoxypyridin-2-yl)-
(4-nitrophenyl)methanol (742mg) as pale yellow crystals.
m.p.137-138°C

¹H-NMR (200MHz, CDCl₃) δ 3.81 (3H, s), 5.64 (1H, d, J=6.8
20 Hz), 6.02 (1H, d, J=6.8 Hz), 7.17 (1H, dd, J=8.4, 1.4 Hz),
7.27 (1H, dd, J=8.4, 4.6 Hz), 7.58 (2H, dd, J=7.0, 2.0 Hz),
8.15 (2H, dd, J=7.0, 2.0 Hz), 8.21 (1H, dd, J=4.6, 1.4 Hz).
IR (KBr) 3348, 1524, 1464, 1344, 1284, 1053, 1020, 837, 797,
744, 689 cm⁻¹

25 Elemental Analysis for C₁₃H₁₂N₂O₄

Calcd. C, 60.00 ; H, 4.65 ; N, 10.76 :

Found. C, 59.97 ; H, 4.57 ; N, 10.82.

Reference Example 114

A mixture of (3-methoxypyridin-2-yl)-(4-nitro-
30 phenyl)methanol (600mg) and 5% Pd-C (0.06g) in ethanol
(20ml) was vigorously stirred under hydrogen atmosphere for
3 hours, and the Pd-C was filtered off. The filtrate was
concentrated under reduced pressure to give (4-amino-
phenyl)-(3-methoxypyridin-2-yl)-methanol (483mg) as pale
35 yellow crystals.

¹H-NMR (200MHz, CDCl₃) δ 3.51-3.65 (2H, m), 3.75 (3H, s),

5.33 (1H, d, J=7.1 Hz), 5.85 (1H, d, J=7.1 Hz), 6.60 (2H, dd, J=6.6, 1.8 Hz), 7.08-7.23 (4H, m), 8.17 (1H, dd, J=4.6, 1.4 Hz).

IR (KBr) 3458, 3463, 3323, 1626, 1614, 1518, 1454, 1427, 1279, 1178, 1038, 835, 804 cm^{-1}

Reference Example 115

A solution of diethyl benzylphosphonate (25g) in methanol (10ml) and concentrated hydrochloric acid (500ml) solution was refluxed for 4 days. The mixture was cooled to room temperature, and precipitated crystal was collected by filtration to give benzylphosphonic acid (11.17g) as colorless crystals.

m.p. 171-173°C

$^1\text{H-NMR}$ (200MHz, DMSO- d_6) δ 2.96 (2H, d, J=21.6 Hz), 7.13-7.34 (5H, m).

IR (KBr) 2779, 2330, 1497, 1458, 1263, 1074, 993, 943, 781, 694, 527, 428 cm^{-1}

Elemental Analysis for $\text{C}_7\text{H}_9\text{O}_3\text{P}$

Calcd. C, 48.85 ; H, 5.27 ; P, 18.00 ;

Found. C, 48.75 ; H, 5.01 ; P, 17.78.

Reference Example 116

Under nitrogen atmosphere, to a mixture of magnesium (3.39g) and a piece of iodine in diethylether (16ml) was dropwise added a solution of 1,4-dibromobutane (5.55ml) and 1,2-dibromoethane (2ml) in diethylether (80ml) at 40°C for 1 hour. The mixture was refluxed for 1 hour, cooled to room temperature and allowed to stand for 2 hours. The upper layer of diethylether was removed through cannula, to obtain the di-Grignard reagent, which was dissolved in dichloro-methane (210ml). The resulting di-Grignard reagent as it is was used for the following reaction. To benzyl phosphonate (8.0g) was added thionyl chloride (40ml) and then 2 drops of DMF, and the mixture was refluxed for 4 hours and concentrated under reduced pressure. The residue was dissolved in dichloromethane (210ml), and the mixture was cooled to 0°C. To the mixture was dropwise added

a solution of the above di-Grignard reagent in dichloromethane, which was cooled to 0°C, through cannula for 1 hour, and the mixture was stirred at room temperature for 16 hours. To the reaction mixture were added 10% ammonium chloride solution (100ml) and saturated sodium chloride solution, and the mixture was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:4) to give 1-benzyl-phosphorane-1-oxide (4.83g) as colorless crystals. ¹H-NMR (200MHz, CDCl₃) δ 1.40-2.08 (8H, m), 3.27 (2H, d, J=15.0 Hz), 7.11-7.42 (5H, m).

IR (KBr) 2951, 1643, 1495, 1454, 1406, 1265, 1236, 1165, 1120, 702 cm⁻¹

Reference Example 117

To 1-benzylphosphorane-1-oxide (4.17g) were added nitric acid (1.7ml) and sulfuric acid (11ml) at 0°C, and the mixture was stirred at 50-60°C for 2 hours. The reaction mixture was added to crushed ice and neutralized with ammonia solution. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. Under reduced pressure, The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:4→1:1) to give 1-(4-nitro-benzyl)phosphorane-1-oxide (2.22g) as yellow crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.55-2.13 (8H, m), 3.32 (2H, d, J=13.8 Hz), 7.50 (2H, dd, J=8.8, 1.8 Hz), 8.22 (2H, d, J=8.8 Hz).

IR (KBr) 3402, 2954, 1514, 1346, 1171, 860, 700 cm⁻¹

Reference Example 118

A mixture of 1-(4-nitrobenzyl)phosphorane-1-oxide (1.80g) and 10% Pd-C (0.2g) in ethanol (30ml) was vigorously stirred under hydrogen atmosphere for 24 hours, and the

catalyst was filtered off. The filtrate was concentrated and purified with column chromatography (ethanol/ethyl acetate=1:2) and recrystallized from ethanol-diethylether to give 1-(4-aminobenzyl)phosphorane-1-oxide (0.90g) as colorless crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.32-2.02 (8H, m), 3.16 (2H, d, J=14.6 Hz), 3.52-3.74 (2H, m), 6.65 (2H, d, J=8.4 Hz), 7.04 (2H, dd, J=8.4, 2.2 Hz).

IR (KBr) 3386, 3338, 3228, 1641, 1612, 1516, 1296, 1263, 1174, 1124, 833 cm⁻¹

Reference Example 119

Under nitrogen atmosphere, to a solution of 2-bromo-3-methoxymethoxypyridine (10.00g) in diethylether (150ml) was added a solution of n-butyllithium in hexane (1.6M, 31.5ml) at -78°C, and the mixture was stirred for 1 hour to prepare the lithium salt. The resulting lithium salt was dropwise added to a solution of 4-nitrobenzaldehyde (6.93g) in tetrahydrofuran (100ml) cooled at -78°C, and the mixture was stirred at the same temperature for 3 hours. To the reaction mixture was added water to stop the reaction, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:3→1:2) to give (3-methoxymethoxypyridin-2-yl)-(4-nitrophenyl)-methanol (11.78g) as yellow oil.

¹H-NMR (200MHz, CDCl₃) δ 3.27 (3H, s), 5.12 (1H, d, J=7.0 Hz), 5.20 (1H, d, J=7.0 Hz), 5.70 (1H, d, J=7.0 Hz), 6.02 (1H, d, J=7.0 Hz), 7.25 (1H, dd, J=8.4, 4.4 Hz), 7.42 (1H, dd, J=8.4, 1.4 Hz), 7.58 (2H, d, J=8.8 Hz), 8.15 (2H, d, J=8.8 Hz), 8.27 (1H, dd, J=4.4, 1.4 Hz).

IR (neat) 3390, 1522, 1448, 1348, 1155, 1084, 1055, 980, 824, 849, 800, 744, 700 cm⁻¹

Reference Example 120

A mixture of (3-methoxymethoxypyridin-2-yl)-(4-

nitrophenyl)methanol (11.78g) and 10% Pd-C (1.2g) in ethanol (100ml) was vigorously stirred under hydrogen atmosphere for 24 hours. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:1→2:1) to give 2-(4-aminobenzyl)-3-methoxymethoxypyridine (2.92g) as orange oil.

¹H-NMR (200MHz, CDCl₃) δ 3.37 (3H, s), 4.08 (2H, s), 5.16 (2H, s), 6.59 (2H, dd, J=8.4, 2.0 Hz), 7.04-7.19 (3H, m), 7.33 (1H, dd, J=8.4, 1.2 Hz), 8.18 (1H, dd, J=4.8, 1.2 Hz). IR (neat) 3433, 3352, 3219, 1620, 1514, 1446, 1265, 1153, 1082, 985, 922, 798 cm⁻¹

Reference Example 121

Under nitrogen atmosphere, to a mixture of magnesium (3.2g) and a piece of iodine in diethylether (20ml) was dropwise added to a solution of 1,5-dibromopentane (13.21g) and 1,2-dibromoethane (1.21ml) in diethylether (80ml) at 40°C for 1 hour. The mixture was refluxed for 1 hour, cooled to room temperature and allowed to stand for 2 hours. The upper layer of diethylether was removed through cannula, to obtain the di-Grignard reagent, which was dissolved in dichloromethane (250ml). The resulting di-Grignard reagent as it is was used for the following reaction. To benzylphosphonic acid (10.0g) was added thionyl chloride (30ml) and then a drop of DMF, and the mixture was refluxed for 3 hours and concentrated under reduced pressure. The residue was dissolved in dichloromethane (210ml), and the mixture was cooled to 0°C. To the mixture was dropwise added a solution of the above di-Grignard reagent in dichloromethane, which was cooled to 0°C, through cannula for 1 hour, and the mixture was stirred at room temperature for 20 hours. To the reaction mixture were added 10% ammonium chloride solution (100ml) and saturated sodium chloride solution, and the mixture was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried with magnesium

sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:3→1:2) to give 1-benzylphosphorinane-1-oxide (5.39g) as colorless crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.36-2.18 (10H, m), 3.17 (2H, d, J=14.0 Hz), 7.23-7.42 (5H, m).

IR (KBr) 2939, 2912, 2886, 1493, 1452, 1404, 1232, 1161, 827, 700 cm⁻¹

10 Reference Example 122

To a solution of diethyl benzylphosphonate (2.5g) in tetrahydrofuran (500ml) was added Red-Al (70% toluene solution) (3.8g) at room temperature, and the mixture was stirred until gas production stopped. To the reaction mixture was added 1,5-dibromopentane (25.18g), and the mixture was stirred at 50-60°C for 16 hours. To the reaction mixture was added water (20ml), and precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was separated and purified with column chromatography (ethyl acetate→ethanol:ethyl acetate=1:2) to give 1-benzylphosphorinane-1-oxide (8.41g) as colorless crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.36-2.18 (10H, m), 3.17 (2H, d, J=14.0 Hz), 7.23-7.42 (5H, m).

25 IR (KBr) 2939, 2912, 2886, 1493, 1452, 1404, 1232, 1161, 827, 700 cm⁻¹

Reference Example 123

To 1-benzylphosphorinane-1-oxide (5.39g) were added nitric acid (1.94ml) and sulfuric acid (15ml) at 0°C, and the mixture was stirred at 50-60°C for 2 hours. The reaction mixture was added to crushed ice-water, neutralized with ammonia solution and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethanol/ethyl

acetate=1:3→1:2) to give 1-(4-nitrobenzyl)-

phosphorinane-1-oxide (2.47g) as pale yellow crystals .

¹H-NMR (200MHz, CDCl₃) δ 1.46-2.18 (10H, m), 3.28 (2H, d, J=13.6 Hz), 7.48 (2H, dd, J=8.8, 2.2 Hz), 8.21 (2H, d, J=8.8 Hz).

IR (KBr) 2926, 1599, 1516, 1348, 1230, 1159, 1132, 864, 822, 696 cm⁻¹

Reference Example 124

A mixture of 1-(4-nitrobenzyl)phosphorinane-1-oxide (2.25g) and 10% Pd-C (0.2g) in ethanol (30ml) was vigorously stirred under hydrogen atmosphere for 24 hours. The catalyst was filtered off, and the filtrate was concentrated and recrystallized from ethanol-diethylether to give 1-(4-aminobenzyl)-phosphorinane-1-oxide (1.5g) as pale yellow crystals.

¹H-NMR (200MHz, CDCl₃) δ 1.27-2.16 (10H, m), 3.06 (2H, d, J=13.8 Hz), 3.53-3.80 (2H, m), 6.65 (2H, d, J=8.3 Hz), 7.05 (2H, dd, J=8.3, 2.0 Hz).

IR (KBr) 3386, 3334, 3224, 2939, 1639, 1612, 1514, 1296, 1225, 1153, 1120, 841 cm⁻¹

Reference Example 125

Under argon atmosphere, to a solution of 4-ethylbromobenzene (10.0g) in tetrahydrofuran (60ml) was added n-butyllithium (1.6M hexane solution) (37.2ml) at -78°C, and the mixture was stirred for 1 hour. To the reaction mixture was dropwise added a solution of tributyl borate (13.68g) in tetrahydrofuran (30ml), and the reaction mixture was warmed to room temperature and stirred at room temperature for 2 hours. To the reaction mixture was added 10% sulfuric acid (100ml), and the mixture was stirred for 1 hour. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in acetone (30ml), and to the mixture was added 10% sulfuric acid (50ml). The mixture was stirred at room temperature

for 16 hours, and under reduced pressure acetone was evaporated. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:2) to give crude 4-ethylphenyl borate (0.91g) as colorless solid. Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), the above crude 4-ethylphenyl borate (0.32g) and potassium carbonate (0.49g) in toluene-ethanol-water (20-2-2ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenyl)-phosphinepalladium (0.06g), and the mixture was refluxed for 18 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:15) to give ethyl 7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (464mg) as colorless crystals. m.p. 81-83°C

¹H-NMR (200MHz, CDCl₃) δ 1.28 (3H, t, J=7.6 Hz), 1.36 (3H, t, J=7.2 Hz), 2.69 (2H, q, J=7.6 Hz), 3.00 (2H, t, J=5.2 Hz), 4.29 (2H, q, J=7.2 Hz), 4.30 (2H, t, J=5.2 Hz), 7.04 (1H, d, J=8.4 Hz), 7.27 (2H, d, J=8.6 Hz), 7.44-7.51 (3H, m), 7.55 (1H, d, J=2.6 Hz), 7.65 (1H, br s).

IR (KBr) 1699, 1493, 1302, 1254, 1213, 1012, 822 cm⁻¹

Elemental Analysis for C₂₁H₂₂O₃

Calcd. C, 78.23 ; H, 6.88 ;

Found. C, 78.05 ; H, 6.61.

Reference Example 126

To a solution of ethyl 7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (430mg) in ethanol (20ml) was added 1N sodium hydroxide (4.0ml) at room temperature, and the mixture was stirred for 24 hours and

- concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (15ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated to give crystals, which were collected by filtration to give 7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (328mg) as colorless crystals.
- m.p. 241-243°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.28 (3H, t, J=7.8 Hz), 2.70 (2H, q, J=7.8 Hz), 3.02 (2H, t, J=4.8 Hz), 4.33 (2H, t, J=4.8 Hz), 7.05 (1H, d, J=8.4 Hz), 7.27 (2H, d, J=8.0), 7.46-7.56 (4H, m), 7.78 (1H, br s).
- IR (KBr) 2966, 1689, 1491, 1437, 1263, 1230, 822 cm⁻¹
- Elemental Analysis for C₁₉H₁₈O₃
- Calcd. C, 77.53 ; H, 6.16 ;
- Found. C, 77.52 ; H, 6.27.
- Reference Example 127

- Under argon atmosphere, to a solution of 4-tert-butylbromobenzene (10.0g) in diethylether (50ml) was added n-butyllithium (1.6M, hexane solution) (32.3ml) at -78°C, and the mixture was stirred for 1 hour. To the reaction mixture was dropwise added trimethyl boric acid (16ml) in diethylether (30ml), and the mixture was warmed to room temperature and stirred at room temperature 16 hours. To the reaction mixture were added 1N hydrochloric acid (50ml) and water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:9) to give crude 4-tert-phenyl borate(0.84g) as pale yellow oil. Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), the above crude 4-tert-butylphenyl borate(0.59g) and potassium carbonate (0.47g) in toluene-ethanol-water

- (20-2-2ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine) palladium (0.06g), and the mixture was refluxed for 20 hours and cooled to room temperature. The organic layer was
- 5 washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:19) to give ethyl
- 10 7-(4-tert-butyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (504mg) as colorless oil.
- ¹H-NMR (200MHz, CDCl₃) δ 1.36 (9H, s), 1.36 (3H, t, J=7.2 Hz), 3.00 (2H, t, J=4.7 Hz), 4.29 (2H, q, J=7.2 Hz), 4.30 (2H, t, J=4.7 Hz), 7.04 (1H, d, J=8.2 Hz), 7.42-7.56 (6H, m), 7.65 (1H, br s).
- 15 IR (neat) 1731, 1491, 1298, 1246, 1211, 1184, 1090, 1018, 824 cm⁻¹

Reference Example 128

- To a solution of ethyl 7-(4-tert-butylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (503.8mg) in ethanol
- 20 (10ml) was added 1N sodium hydroxide (2.0m) at room temperature, and the mixture was stirred for 64 hours and concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (15ml), and the mixture was extracted with ethyl acetate. The organic layer was washed
- 25 with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The resulting crystal was collected by filtration to give 7-(4-tert-butyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (396mg) as colorless crystals.
- 30 m.p. 259-261°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.37 (9H, s), 3.03 (2H, t, J=4.4 Hz), 4.34 (2H, t, J=4.4 Hz), 7.06 (1H, d, J=8.4 Hz), 7.41-7.58 (6H, m), 7.79 (1H, br s).
- IR (KBr) 2951, 1678, 1489, 1263, 829, 820 cm⁻¹
- 35 Elemental Analysis for C₂₁H₂₂O₃
- Calcd. C, 78.23 ; H, 6.88 :

Found. C, 78.10 ; H, 6.81.

Reference Example 129

Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), 4-chloro-phenyl borate (289mg) and potassium carbonate (464mg) in toluene-ethanol-water (20-2-2ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenyl)-phosphinepalladium (0.06g), and the mixture was refluxed for 24 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:19) to give ethyl 7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (459mg) as colorless crystals.

m.p. 131-134°C

¹H-NMR (200MHz, CDCl₃) δ 1.36 (3H, t, J=7.2 Hz), 3.01 (2H, t, J=5.0 Hz), 4.23-4.34 (4H, m), 7.05 (1H, d, J=8.4 Hz), 7.37-7.52 (6H, m), 7.64 (1H, s).

IR (KBr) 1705, 1485, 1302, 1255, 1213, 820 cm⁻¹

Elemental Analysis for C₁₉H₁₇O₃Cl

Calcd. C, 69.41 ; H, 5.21 ; Cl, 10.78 ;

Found. C, 69.16 ; H, 5.12 ; Cl, 10.85.

Reference Example 130

To a solution of ethyl 7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (400mg) in tetrahydrofuran-ethanol (10-10ml) was added 1N sodium hydroxide (2.0ml) at room temperature, and the mixture was stirred for 42 hours and concentrated under reduced pressure.

To the residue was added 1N hydrochloric acid (15ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The resulting crystal was collected by filtration to give 7-(4-chlorophenyl)-2,3-dihydro-1-benzoxepine-4-

carboxylic acid (342mg) as colorless crystals.

m.p. 263-264°C

¹H-NMR (200MHz, CDCl₃) δ 3.03 (2H, t, J=4.7 Hz), 4.34 (2H, t, J=4.7 Hz), 7.07 (1H, d, J=8.4 Hz), 7.35-7.55 (6H, m),
5 7.76 (1H, br s).

IR (KBr) 2959, 1680, 1483, 1267, 1230, 818 cm⁻¹

Elemental Analysis for C₁₇H₁₃O₃Cl

Calcd. C, 69.89 ; H, 4.36 ; Cl, 11.79 ;

Found. C, 67.55 ; H, 4.19 ; Cl, 11.46.

10 Reference Example 131

Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), 4-trifluoromethylphenyl borate (351.5mg) and potassium carbonate (0.47g) in toluene-ethanol-water (20-2-2ml) was
15 stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.06g), and the mixture was refluxed for 20 hours and cooled to room temperature. The organic layer was washed with
20 saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:10) to give ethyl 7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (489mg) as colorless crystals.

25 m.p. 107-110°C

¹H-NMR (200MHz, CDCl₃) δ 1.37 (3H, t, J=7.2 Hz), 2.99-3.05 (2H, m), 4.29 (2H, q, J=7.2 Hz), 4.33 (2H, t, J=4.8 Hz), 7.09 (1H, d, J=8.4 Hz), 7.49 (1H, dd, J=8.4, 2.4 Hz), 7.58 (1H, d, J=2.4 Hz), 7.62-7.73 (5H, m).

30 IR (KBr) 1701, 1329, 1257, 1126, 1107, 1068, 1012, 822 cm⁻¹

Elemental Analysis for C₂₀H₁₇O₃F₃

Calcd. C, 66.30 ; H, 4.73 ; F, 15.73 ;

Found. C, 66.40 ; H, 4.63 ; F, 15.44.

Reference Example 132

35 To a solution of ethyl 7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (440mg) in

tetrahydrofuran-ethanol (10-10ml) was added 1N sodium hydroxide (4.0ml) at room temperature, and the mixture was stirred for 20 hours and concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (5ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The resulting crystal was collected by filtration to give 7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (392mg) as colorless crystals.

m.p. 273-276°C

¹H-NMR (200MHz, DMSO-d₆) δ 2.89 (2H, t, J=4.4 Hz), 4.28 (2H, t, J=4.4 Hz), 7.09 (1H, d, J=8.4 Hz), 7.61-7.70 (2H, m), 7.78 (2H, d, J=8.4 Hz), 7.92-7.96 (3H, m).

IR (KBr) 2979, 1689, 1329, 1263, 1134, 1072, 831 cm⁻¹

Elemental Analysis for C₁₈H₁₃O₃F₃

Calcd. C, 64.67 ; H, 3.92 ;

Found. C, 64.62 ; H, 3.89.

Reference Example 133

Under argon atmosphere, to a solution of 4-bromophenetole (26.4g) in tetrahydrofuran (200ml) was dropwise added n-butyl-lithium (1.6M, hexane solution) (90.3ml) at -78°C for 50 minutes, and the mixture was stirred for 30 minutes. To the reaction mixture was dropwise added a solution of trimethyl borate (40.8g) in tetrahydrofuran (40ml) for 30 minutes, and the mixture was stirred for 30 minutes, warmed to room temperature, and further stirred for 1.5 hours. To the reaction mixture was added 10% sulfuric acid (182ml) for 40 minutes or more, and the mixture was stirred 1.5 hours, extracted with ethyl acetate, washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diisopropylether-hexane to give 4-ethoxyphenyl borate (15.5g) as colorless crystals.

Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (504.5mg), the

above 4-ethoxyphenyl borate (310mg) and potassium carbonate (0.47g) in toluene-ethanol-water (20-2-2ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.06g), and the mixture was refluxed for 20 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:9→1:5) to give ethyl 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (468mg) as colorless crystals.

m.p. 124-127°C

¹H-NMR (200MHz, CDCl₃) δ 1.36 (3H, t, J=7.2 Hz), 1.44 (3H, t, J=7.0 Hz), 3.00 (2H, t, J=4.0 Hz), 4.08 (2H, q, J=7.0 Hz), 4.28 (2H, q, J=7.2 Hz), 4.30 (2H, t, J=4.0 Hz), 6.96 (2H, dd, J=6.6, 2.2 Hz), 7.02 (1H, d, J=8.4 Hz), 7.41 (1H, d, J=2.6 Hz), 7.44-7.51 (3H, m), 7.65 (1H, br s).

IR (KBr) 1701, 1493, 1254, 1215, 1014, 824 cm⁻¹

Elemental Analysis for C₂₁H₂₂O₄

Calcd. C, 74.54 ; H, 6.55 ;

Found. C, 74.42 ; H, 6.47.

Reference Example 134

To a solution of ethyl 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (447.8mg) in ethanol (20ml) was added 2N sodium hydroxide (2.0ml) at room temperature, and the mixture was stirred for 20 hours and concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (5ml), and the mixture was extracted with ethyl acetate and concentrated. The resulting crystal was collected by filtration to give 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (380mg) as colorless crystals.

m.p. 269-271°C

¹H-NMR (200MHz, DMSO-d₆) δ 1.35 (3H, t, J=7.0 Hz), 2.81-2.94 (2H, m), 4.06 (2H, q, J=7.0 Hz), 4.18-4.31 (2H, m),

6.94-7.00 (3H, m), 7.49-7.79 (5H, m).

IR (KBr) 2980, 1678, 1610, 1493, 1431, 1265, 1232, 1182, 1049, 926, 829, 810 cm^{-1}

Elemental Analysis for $\text{C}_{11}\text{H}_{10}\text{O}$.

5 Calcd. C, 73.53 ; H, 5.85 :

Found. C, 73.44 ; H, 5.77.

Reference Example 135

Under argon atmosphere, to a solution of 4-trifluoromethoxybromobenzene (10.0g) in tetrahydrofuran (75ml) was
10 dropwise added n-butyllithium (1.6M, hexane solution) (28.5ml) at -78°C for 20 minutes, and the mixture was stirred for 40 minutes. To the reaction mixture was dropwise added a solution of trimethyl borate (12.9g) in tetrahydrofuran (12ml) for 15 minutes, and the mixture was stirred at -
15 78°C for 30 minutes and at room temperature for 1 hour. To the reaction mixture was added was dropwise added 10% sulfuric acid (57.6ml) for 15 minutes, and the mixture was stirred for 2 hours, extracted with ethyl acetate, washed with saturated sodium chloride solution, dried with
20 magnesium sulfate and concentrated under reduced pressure.

The residue was crystallized from hexane to give 4-trifluoromethoxyphenyl borate (2.7g) as colorless crystals.

Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), the
25 above 4-trifluoromethoxyphenyl borate (380mg) and potassium carbonate (0.46g) in toluene-ethanol-water (20-2-2ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.06g), and the mixture was refluxed
30 for 18 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:10) to give
35 ethyl 7-(4-trifluoromethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (379mg) as colorless crystals.

m.p. 59-63°C.

¹H-NMR (200MHz, CDCl₃) δ 1.36 (3H, t, J=7.1 Hz), 3.01 (2H, t, J=4.8 Hz), 4.24-4.34 (4H, m), 7.06 (1H, d, J=8.4 Hz), 7.22-7.31 (2H, m), 7.44 (1H, dd, J=8.4, 2.2 Hz), 7.52 (1H, d, J=2.2 Hz), 7.57 (2H, d, J=8.8 Hz), 7.64 (1H, br s).
IR (KBr) 1701, 1489, 1304, 1257, 1227, 1211, 1182, 1134, 1014, 833, 808 cm⁻¹

Elemental Analysis for C₂₀H₁₇O₄F₃

Calcd. C, 63.49 ; H, 4.53 ;

10 Found. C, 63.68 ; H, 4.47.

Reference Example 136

To a solution of ethyl 7-(4-trifluoromethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (323.9mg) in tetrahydrofuran-ethanol (5-5ml) was added 1N sodium hydroxide (2.0ml) at room temperature, and the mixture was stirred for 5 days and concentrated under reduced pressure. To the residue 1N hydrochloric acid (5ml) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The resulting crystal was collected by filtration to give 7-(4-trifluoromethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (282mg) as colorless crystals.

m.p. 252-254°C

25 ¹H-NMR (200MHz, CDCl₃) δ 3.03 (2H, t, J=4.6 Hz), 4.34 (2H, t, J=4.6 Hz), 7.08 (1H, d, J=8.4 Hz), 7.28 (2H, d, J=8.8 Hz), 7.47 (1H, dd, J=8.4, 2.2 Hz), 7.54 (1H, d, J=2.2 Hz), 7.59 (2H, d, J=8.8 Hz), 7.78 (1H, br s).

IR (KBr) 2981, 1691, 1493, 1290, 1261, 1213, 1169, 835 cm⁻¹

30 Elemental Analysis for C₁₈H₁₃O₄F₃

Calcd. C, 61.72 ; H, 3.74 ; F, 16.27 ;

Found. C, 61.61 ; H, 3.72 ; F, 16.06.

Reference Example 137

To a solution of 5-bromosalicylaldehyde (10.0g) and tert-butyl acrylate (17.5ml) in tert-butanol (100ml) was added potassium tert-butoxide (1.67g) at room temperature,

and the mixture was refluxed for 66 hours and cooled to room temperature. To the mixture was added ethyl acetate, and the mixture was washed with water, 1N sodium hydroxide and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:19) to give tert-butyl 6-bromo-2H-1-benzopyran-3-carboxylate (10.86g) as pale yellow crystals.
m.p. 96-97°C

¹H-NMR (200MHz, CDCl₃) δ 1.53 (9H, s), 4.95 (2H, d, J=0.8 Hz), 6.72 (1H, d, J=8.4 Hz), 7.21-7.30 (3H, m).

IR (KBr) 1699, 1479, 1331, 1288, 1159, 1088, 816 cm⁻¹

Elemental Analysis for C₁₄H₁₅O₃Br

Calcd. C, 54.04 ; H, 4.86 ; Br, 25.68 :

Found. C, 53.98 ; H, 4.86 ; Br, 25.90.

Reference Example 138

Under argon atmosphere, a solution of tert-butyl 6-bromo-2H-1-benzopyran-3-carboxylate (5.00g), 4-methylphenyl borate (2.62g) and potassium carbonate (4.44g) in toluene-ethanol-water (160-16-16ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.56g), and the mixture was refluxed for 14 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:19) to give pale yellow crystals, which were recrystallized from ethanol to give tert-butyl 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylate (3.84g) as pale yellow crystals.
m.p. 80-82°C

¹H-NMR (200MHz, CDCl₃) δ 1.54 (9H, s), 2.39 (3H, s), 4.98 (2H, d, J=1.4 Hz), 6.94 (1H, d, J=8.2 Hz), 7.23 (2H, d, J=8.0 Hz), 7.33 (1H, d, J=2.2 Hz), 7.36-7.45 (4H, m).

IR (KBr) 1705, 1367, 1340, 1311, 1251, 1159, 1133, 1003, 808 cm⁻¹

Elemental Analysis for $C_{21}H_{22}O_3$

Calcd. C, 78.23 ; H, 6.88 :

Found. C, 78.07 ; H, 6.89.

Reference Example 139

- 5 To tert-butyl 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylate (3.00g) was added 4N hydrochloric acid-ethyl acetate (10ml) at room temperature, and the mixture was stirred for 16 hours. To the reaction mixture was added hexane, and crystal was collected by filtration and washed
10 with hexane to give 6-(4-methylphenyl)-2H-1-benzopyran-3-carboxylic acid (2.14g) as pale yellow crystals.
m.p. 236-237°C

1H -NMR (200MHz, $CDCl_3$) δ 2.40 (3H, s), 5.05 (2H, d, $J=1.4$ Hz), 6.94 (1H, d, $J=8.2$ Hz), 7.23-7.27 (2H, m), 7.37 (1H, d, $J=2.2$ Hz), 7.41-7.52 (3H, m), 7.63 (1H, br s).

- 15 IR (KBr) 3022, 1689, 1633, 1485, 1442, 1306, 1242, 812 cm^{-1}

Elemental Analysis for $C_{17}H_{14}O_3$

Calcd. C, 76.68 ; H, 5.30 :

Found. C, 76.51 ; H, 5.03.

- 20 Reference Example 140

- To a solution of 5-bromo-salicylaldehyde (10.0g) and ethyl crotonate (11.36g) in tert-butanol (50ml) was added potassium tert-butoxide (1.12g) at room temperature, and the mixture was refluxed for 3 days. To the reaction mixture
25 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:10→1:5) to
30 give pale yellow liquid (5.75g). The resulting compound was used for the following reaction without subjecting to further purification. Under nitrogen atmosphere, to a solution of the above crude product (5.5g) and triethylamine (7.3ml) in dichloro-methane (50ml) was added methane-
35 sulfonyl chloride (2.0ml) at 0°C, and the mixture was stirred at 0°C for 10 minutes and then at room temperature for 18

hours. To the reaction mixture was added water, and the mixture was extracted with diethylether. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:15) to give crude product (4.85g) as pale yellow oil. The resulting compound was used for the following reaction without subjecting to further purification. Under argon atmosphere, a solution of the above crude product (4.7g), 4-methylphenyl borate (2.58g) and potassium carbonate (4.4g) in toluene-ethanol-water (160-16-16ml) was stirred at room temperature for 1 hour.

To the reaction mixture was added tetrakis(triphenyl)phosphinepalladium (0.54g), and the mixture was refluxed for 20 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:15) to give ethyl 6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxylate (3.63g) as pale yellow crystals.

m.p. 82-84°C

¹H-NMR (200MHz, CDCl₃) δ 1.35 (3H, t, J=7.2 Hz), 1.40 (3H, d, J=6.6 Hz), 2.39 (3H, s), 4.29 (2H, q, J=7.2 Hz), 5.40 (1H, q, J=6.6 Hz), 6.92 (1H, d, J=8.4 Hz), 7.24 (2H, d, J=8.2 Hz), 7.36 (1H, d, J=2.2 Hz), 7.40-7.49 (4H, m).

IR (KBr) 1699, 1485, 1296, 1244, 1217, 1190, 1136, 1047, 804, 764, 511 cm⁻¹

Elemental Analysis for C₂₀H₂₀O₃

Calcd. C, 77.90 ; H, 6.54 ;

Found. C, 77.79 ; H, 6.46.

Reference Example 141

To a solution of ethyl 6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxylate (3.0g) in ethanol-tetrahydrofuran (30-30ml) was added 1N sodium hydroxide (12ml) at room temperature, and the mixture was stirred for 16 hours.

Under reduced pressure, the solvent was evaporated and acidified with 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 6-(4-methylphenyl)-2-methyl-2H-1-benzopyran-3-carboxylic acid (2.15g) as yellow crystals. m.p. 190-192°C

¹H-NMR (200MHz, CDCl₃) δ 1.43 (3H, d, J=6.6 Hz), 2.39 (3H, s), 5.40 (1H, q, J=6.6 Hz), 6.94 (1H, d, J=8.4 Hz), 7.24 (2H, d, J=8.0 Hz), 7.38 (1H, d, J=2.2 Hz), 7.44 (2H, d, J=8.0 Hz), 7.50 (1H, dd, J=8.4, 2.2 Hz), 7.60 (1H, s).

IR (KBr) 2983, 1680, 1635, 1485, 1421, 1298, 1261, 1190, 808 cm⁻¹

Elemental Analysis for C₁₈H₁₆O₃

Calcd. C, 77.12 ; H, 5.75 ;

Found. C, 77.25 ; H, 5.63.

Reference Example 142

A solution of 5-bromo-2-thiophenecarboxyaldehyde (6.08g) and methyl (triphenylphosphoranilidene)acetate (11.12g) in toluene (60ml) was refluxed under nitrogen atmosphere for 2 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:15→1:9) and recrystallized from ethyl acetate to give methyl (E)-3-(5-bromothiophen-2-yl)-acrylate (7.44g) as pale yellow crystals.

m.p. 60-62°C

¹H-NMR (200MHz, CDCl₃) δ 3.79 (3H, s), 6.13 (1H, d, J=15.8 Hz), 6.96-7.05 (2H, m), 7.66 (1H, d, J=15.8 Hz).

IR (KBr) 1724, 1624, 1417, 1257, 1203, 1165, 968, 802, 486 cm⁻¹

Elemental Analysis for C₈H₆O₂SBBr

Calcd. C, 38.88 ; H, 2.86 ; S, 12.98 ; Br, 32.34 :
Found. C, 38.95 ; H, 2.83 ; S, 13.13 ; Br, 32.36.

Reference Example 143

Under argon atmosphere, a solution of methyl (E)-
5 3-(5-bromothiophen-2-yl)acrylate (4.0g), 4-methylphenyl
borate (2.64g) and potassium carbonate (4.48g) in
toluene-ethanol-water (160-16-16ml) was stirred at room
temperature for 1 hour. To the reaction mixture was added
tetrakistriphenylphosphinepalladium (0.56g), and the
10 mixture was refluxed for 16 hours and cooled to room
temperature. The organic layer was washed with saturated
sodium chloride solution, dried with magnesium sulfate and
concentrated under reduced pressure to give crude product
(5.24g). To a solution of the resulting carboxylic acid
15 ester (5.24g) in tetrahydrofuran (100ml) was added 1N sodium
hydroxide (20ml) at room temperature, and the mixture was
stirred for 5 days. To the reaction mixture was added water,
and the mixture was washed with ethyl acetate. The aqueous
layer was acidified with concentrated hydrochloric acid,
20 and the mixture was extracted with ethyl acetate, washed
with saturated sodium chloride solution, dried with
magnesium sulfate and concentrated under reduced pressure
to give (E)-3-[5-(4-methylphenyl)-thiophen-2-yl]acrylic
acid (1.9g) as yellow crystals.
25 m.p. 223-225°C

¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 6.21 (1H, d, J=15.8
Hz), 7.16-7.27 (4H, m), 7.52 (2H, d, J=8.0 Hz), 7.84 (1H,
d, J=15.8 Hz).

IR (KBr) 2968, 1666, 1606, 1413, 1261, 1230, 804 cm⁻¹

30 Elemental Analysis for C₁₁H₁₂O₂S

Calcd. C, 38.83 ; H, 4.95 ; S, 13.12 :

Found. C, 38.76 ; H, 5.07 ; S, 13.28.

Reference Example 144

To a suspension of 5-bromo-2-furancarboxylic acid
35 (5.00g) and N-hydroxysuccinimide (3.31g) in acetonitrile
(50ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)-

carbodiimide hydrochloride (5.52g) at room temperature, and the mixture was stirred for 2 hours. To the reaction mixture was added a suspension of N,O-dimethylhydroxyl-amine hydrochloride (2.81g) and triethylamine (10ml) in
5 acetonitrile (20ml), and the mixture was stirred for 1 hour. To the reaction mixture were added 1,8-diazabicyclo-[5.4.0]-7-undecene (4.3ml) and DMF (50ml), and the mixture was stirred for 3 hours and concentrated under reduced pressure. To the residue was added water, and the mixture
10 was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:4→1:3→1:2) to
15 give N-methyl-N-methoxy-5-bromofuran-2-carboxamide (2.77g) as pale yellow oil.

¹H-NMR (200MHz, CDCl₃) δ 3.34 (3H, s), 3.77 (3H, s), 6.45 (1H, d, J=3.6 Hz), 7.09 (1H, d, J=3.6 Hz).

IR (neat) 2974, 2937, 1647, 1475, 1416, 1385, 1211, 1024,
20 985, 926, 796, 739 cm⁻¹

Reference Example 145

Under argon atmosphere, a solution of N-methyl-N-methoxy-5-bromofuran-2-carboxamide (2.77g), 4-methyl-phenyl borate (1.93g) and potassium carbonate (3.27g) in
25 toluene-ethanol-water (110-11-11ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.41g), and the mixture was refluxed for 20 hours and cooled to room temperature. The organic layer was washed with saturated
30 sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:5→1:2→1:1) to give N-methyl-N-methoxy-5-(4-methylphenyl)furan-2-carboxamide (2.65g) as
35 colorless crystals.

m.p. 54-58°C

¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 3.38 (3H, s), 3.82 (3H, s), 6.69 (1H, d, J=3.8 Hz), 7.20-7.26 (3H, m), 7.68 (2H, d, J=8.6 Hz).

IR (neat) 1632, 1487, 1381, 1032, 987, 798, 739, 557, 494 cm⁻¹

Elemental Analysis for C₁₄H₁₅NO₃

Calcd. C, 68.56 ; H, 6.16 ; N, 5.71 :

Found. C, 68.22 ; H, 6.02 ; N, 5.47.

Reference Example 146

- 10 Under nitrogen atmosphere, to a solution of N-methyl-N-methoxy-5-(4-methylphenyl)furan-2-carboxamide (2.5g) in tetrahydrofuran (20ml) was added diisobutyl-aluminum hydride (1.01M toluene solution) (15ml) at -78°C, and the mixture was stirred at -78°C for 10 minutes and then
15 at 0°C for 15 minutes. To the reaction mixture was added 1N hydrochloric acid to stop the reaction, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was
20 separated and purified with column chromatography (ethyl acetate/hexane=1:5→1:4) to give crude product (1.49g). A solution of the crude aldehyde (1.49g) and methyl (triphenylphosphoranilidene)acetate (2.67g) in toluene (30ml) was refluxed under nitrogen atmosphere for 1 hour
25 and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column
30 chromatography (ethyl acetate/hexane=1:9→1:5) to give methyl (E)-3-[5-(4-methylphenyl)furan-2-yl]acrylate (1.63g) as pale yellow crystals.

m.p. 113-115°C

- 35 ¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 3.80 (3H, s), 6.39 (1H, d, J=15.5 Hz), 6.68 (2H, s), 7.22 (2H, d, J=8.4 Hz), 7.44 (1H, d, J=15.5 Hz), 7.62 (2H, d, J=8.4 Hz).

IR (KBr) 1716, 1632, 1304, 1201, 1161, 798 cm^{-1}

Elemental Analysis for $\text{C}_{15}\text{H}_{14}\text{O}_3$

Calcd. C, 74.36 ; H, 5.82 ;

Found. C, 74.36 ; H, 5.75.

5 Reference Example 147

To a solution of methyl (E)-3-[5-(4-methylphenyl)-furan-2-yl]acrylate (1.49g) in tetrahydrofuran-ethanol (10-10ml) was added 2N sodium hydroxide (4ml) at room temperature, and the mixture was stirred for 24 hours. The reaction mixture was acidified with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to give (E)-3-[5-(4-methylphenyl)-furan-2-yl]acrylic acid (0.93g) as colorless crystals. m.p. 183-184°C

^1H -NMR (200MHz, CDCl_3) δ 2.39 (3H, s), 6.39 (1H, d, $J=15.4$ Hz), 6.70 (1H, d, $J=3.4$ Hz), 6.75 (1H, d, $J=3.4$ Hz), 7.23 (2H, d, $J=8.2$ Hz), 7.52 (1H, d, $J=15.4$ Hz), 7.64 (1H, d, $J=8.2$ Hz).

IR (KBr) 2964, 1678, 1624, 1419, 1308, 1261, 785 cm^{-1}

Elemental Analysis for $\text{C}_{14}\text{H}_{12}\text{O}_3$

Calcd. C, 73.67 ; H, 5.30 ;

Found. C, 73.42 ; H, 5.15.

25 Reference Example 148

A solution of 4-bromo-2-thiophenecarboxyaldehyde (4.77g) and methyl (triphenylphosphoranilidene)acetate (8.44g) in toluene (50ml) was refluxed under nitrogen atmosphere for 3 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:15) to give methyl (E)-3-(4-bromothiophen-2-yl)acrylate (5.55g) as pale yellow crystals.

m.p. 63-67°C

¹H-NMR (200MHz, CDCl₃) δ 3.80 (3H, s), 6.25 (1H, d, J=15.8 Hz), 7.16 (1H, d, J=0.8 Hz), 7.26 (1H, d, J=0.8 Hz), 7.68 (1H, d, J=15.8 Hz).

5 IR (KBr) 1713, 1630, 1304, 1257, 1165, 958, 828 cm⁻¹

Elemental Analysis for C₁₁H₉O₂SBr

Calcd. C, 38.88 ; H, 2.86 ; S, 12.98 ; Br, 32.34 ;

Found. C, 38.78 ; H, 2.83 ; S, 12.98 ; Br, 32.27.

Reference Example 149

10 Under argon atmosphere, a solution of methyl (E)-3-(4-bromothiophen-2-yl)acrylic acid (3.0g), 4-methylphenyl borate (1.82g) and potassium carbonate (3.36g) in toluene-ethanol-water (120-12-12ml) was stirred at room temperature for 1 hour. To the reaction mixture was added
15 tetrakis(triphenylphosphine)palladium (0.42g), and the mixture was refluxed for 24 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was
20 separated and purified with column chromatography (ethyl acetate/hexane=1:9→1:5→1:2) to give methyl (E)-3-[4-(4-methylphenyl)thiophen-2-yl]acrylate (2.40g) as pale yellow crystals.

m.p. 116-118°C

25 ¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 3.80 (3H, s), 6.27 (1H, d, J=15.8 Hz), 7.21 (2H, d, J=7.8 Hz), 7.43-7.50 (4H, m), 7.80 (1H, d, J=15.8 Hz).

IR (KBr) 1713, 1622, 1506, 1423, 1302, 1240, 1192, 1159, 966, 847, 916, 760 cm⁻¹

30 Elemental Analysis for C₁₁H₁₁O₂S

Calcd. C, 69.74 ; H, 5.46 ; S, 12.41 ;

Found. C, 69.54 ; H, 5.47 ; S, 12.24.

Reference Example 150

To a solution of methyl (E)-3-[4-(4-methylphenyl)-
35 thiophen-2-yl]acrylate (2.40g) in tetrahydrofuran (50ml) was added 2N sodium hydroxide (6.0ml) at room temperature.

- and the mixture was stirred for 6 days. Precipitated crystal was collected by filtration and washed with tetrahydrofuran. To the crystals was added 1N hydrochloric acid (20ml), and the mixture was extracted with ethyl acetate.
- 5 The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to give (E)-3-[4-(4-methylphenyl)thiophen-2-yl]acrylic acid (1.24g) as pale yellow crystals.
- 10 m.p. 206-207°C
- ¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 6.28 (1H, d, J=15.6 Hz), 7.23 (2H, d, J=8.0 Hz), 7.47 (2H, d, J=8.0 Hz), 7.49 (1H, s), 7.55 (1H, d, J=1.4 Hz), 7.90 (1H, d, J=15.6 Hz). IR (KBr) 2970, 2918, 1682, 1622, 1306, 1196, 966, 818, 764 cm⁻¹
- 15 Elemental Analysis for C₁₄H₁₂O₂S
Calcd. C, 68.83 ; H, 4.95 ; S, 13.12 ;
Found. C, 68.66 ; H, 4.77 ; S, 13.08.
Reference Example 151
- 20 Under nitrogen atmosphere, to a solution of ethyl chloroformylbutyrate (25.0g) in 1,2-dichloroethane (150ml) was dropwise added a solution of tin tetrachloride (76.6g) in 1,2-dichloroethane (50ml) at 0°C and then a solution of 2-bromothiophene (22.8g) in 1,2-dichloroethane (20ml), and
- 25 the mixture was stirred at room temperature for 2 hours. The reaction mixture was vigorously stirred and added to ice-concentrated hydrochloric acid to stop the reaction. The mixture was stirred for 30 minutes and extracted with dichloromethane. The organic layer was washed with
- 30 saturated sodium bicarbonate solution and saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:5) to give ethyl 5-(5-bromothiophen-2-yl)-5-oxovalerate (28.1g) as
- 35 colorless crystals.
m.p. 53-54°C

¹H-NMR (200MHz, CDCl₃) δ 1.26 (3H, t, J=7.2 Hz), 1.97-2.12 (2H, m), 2.41 (2H, t, J=7.2 Hz), 2.92 (2H, t, J=7.3 Hz), 4.14 (2H, q, J=7.2 Hz), 7.10 (1H, d, J=4.0 Hz), 7.47 (1H, d, J=4.0 Hz).

5 IR (KBr) 1726, 1664, 1419, 1281, 1184, 980, 812 cm⁻¹

Elemental Analysis for C₁₁H₁₃O₃SBr

Calcd. C, 43.29 ; H, 4.29 ; S, 10.51 ; Br, 26.18 :

Found. C, 43.54 ; H, 4.20 ; S, 10.64 ; Br, 26.24.

Reference Example 152

10 Under argon atmosphere, a solution of ethyl 5-(5-bromothiophen-2-yl)-5-oxovalerate (10.09g), 4-methylphenyl borate (5.39g) and potassium carbonate (9.14g) in toluene-ethanol-water (320-32-32ml) was stirred at room temperature for 1 hour. To the reaction mixture was added
15 tetrakis(triphenylphosphine)palladium (1.14g), and the mixture was refluxed for 8 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was
20 separated and purified with column chromatography (ethyl acetate/hexane=1:4→1:3→1:2→1:1) to give ethyl 5-[5-(4-methylphenyl)thiophen-2-yl]-5-oxovalerate (10.23g) as colorless crystals.

m.p. 120-121°C

25 ¹H-NMR (200MHz, CDCl₃) δ 1.26 (3H, t, J=7.2 Hz), 2.01-2.15 (2H, m), 2.38 (3H, s), 2.44 (2H, t, J=7.4 Hz), 2.97 (2H, t, J=7.2 Hz), 4.15 (2H, q, J=7.2 Hz), 7.22 (2H, d, J=7.9 Hz), 7.27 (1H, d, J=4.1 Hz), 7.55 (2H, d, J=7.9 Hz), 7.68 (1H, d, J=4.1 Hz).

30 IR (KBr) 1722, 1647, 1448, 1286, 1173, 816 cm⁻¹

Elemental Analysis for C₁₈H₂₀O₃S

Calcd. C, 68.33 ; H, 6.37 ; S, 10.13 :

Found. C, 68.40 ; H, 6.26 ; S, 10.11.

Reference Example 153

35 To a solution of ethyl 5-[5-(4-methylphenyl)thiophen-2-yl]-5-oxovalerate (4.50g) in trifluoroacetic acid

- (7.66ml) was added triethylsilane(5.7ml) at room temperature, and the mixture was stirred for 4 days. To the reaction mixture was added ethyl acetate, and the mixture was made alkaline with saturated sodium bicarbonate solution.
- 5 The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:9) to give crude ethyl 5-[5-(4-methylphenyl)thiophen-
- 10 2-yl]valerate. To a solution of the crude ethyl 5-[5-(4-methylphenyl)thiophen-2-yl]valerate in tetrahydrofuran (50ml) was added 1N sodium hydroxide (20ml) at room temperature, and the mixture was stirred for 24 hours. To the reaction mixture was added water, and the mixture was
- 15 washed with diethylether. The aqueous layer was acidified with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to
- 20 precipitate crystals, which were collected by filtration and washed with hexane to give 5-[5-(4-methylphenyl)-thiophen-2-yl]valeric acid (2.88g) as colorless crystals. m.p.124-127°C
- ¹H-NMR (200MHz, CDCl₃) δ 1.67-1.82 (4H, m), 2.35 (3H, s),
- 25 2.36-2.45 (2H, m), 2.78-2.90 (2H, m), 6.73 (1H, d, J=3.6 Hz), 7.07 (1H, d, J=3.6 Hz), 7.15 (2H, d, J=8.4 Hz), 7.44 (2H, d, J=8.4 Hz).
- IR (KBr) 2941, 1693, 1512, 1429, 1408, 1317, 1267, 1203, 945, 797, 771 cm⁻¹
- 30 Elemental Analysis for C₁₆H₁₈O₂S
- Calcd. C, 70.04 ; H, 6.61 ; S, 11.69 ;
- Found. C, 69.79 ; H, 6.37 ; N, 11.62.
- Reference Example 154

Under nitrogen atmosphere, to a solution of 5-[5-

35 (4-methylphenyl)thiophen-2-yl]valeric acid (2.60g) in tetrahydrofuran (30ml) was added oxalyl chloride (1.24ml)

at room temperature and then a drop of DMF, and the mixture was stirred 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in dichloromethane (30ml). To the mixture was added tin tetra-chloride (1.5ml) at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to water to stop the reaction, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:9→1:5) to give 2-(4-methylphenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene (2.07g) as pale yellow crystals.

m.p. 82-84°C

¹H-NMR (200MHz, CDCl₃) δ 1.82-2.06 (4H, m), 2.35 (3H, s), 2.71-2.78 (2H, m), 3.06-3.12 (2H, m), 7.17 (2H, d, J=8.2 Hz), 7.44 (2H, d, J=8.2 Hz), 7.57 (1H, s).

IR (KBr) 2927, 1662, 1390, 1176, 810cm⁻¹

Elemental Analysis for C₁₆H₁₆OS

Calcd. C, 74.96 ; H, 6.29 ; S, 12.51 ;

Found. C, 74.89 ; H, 6.20 ; S, 12.53.

Reference Example 155

To a solution of 2-(4-methylphenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene (2.62g) and dimethyl carbonate (2.6ml) in tetrahydrofuran (50ml) was added potassium tert-butoxide (1.38g) at room temperature, and the mixture was refluxed for 1 hour. To the reaction mixture were added potassium tert-butoxide (1.4g) and dimethyl carbonate (5ml), and the mixture was refluxed for 2 hours and cooled to room temperature. To the mixture was added 1N hydrochloric acid (150ml) at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to give crude products (3.30g).

To the crude products (3.30g) in dichloromethane (50ml) was added sodium boron hydride (0.77g) at room temperature and then methanol (8ml) at -15°C for 30 minutes, and the mixture was stirred for 2 hours. To the reaction mixture
5 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to give crude product (2.95g). To a solution of the crude product (2.95g) and
10 triethylamine (7ml) in dichloromethane (20ml) was added methanesulfonyl chloride (1.2ml) at 0°C, and the mixture was stirred at room temperature for 17 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated
15 sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The concentrate was purified with column chromatography (ethyl acetate/hexane=1:9) to give methyl 2-(4-methyl-phenyl)-7,8-dihydro-6H-cyclohepta[b]thiophene-5-carboxylate (884mg) as yellow
20 crystals.
¹H-NMR (200MHz, CDCl₃) δ 1.98-2.11 (2H, m), 2.36 (3H, s), 2.79 (2H, t, J=5.5 Hz), 3.09 (2H, t, J=5.6 Hz), 3.79 (3H, s), 7.08 (1H, s), 7.17 (2H, d, J=8.1 Hz), 7.42 (2H, d, J=8.1 Hz), 7.60 (1H, s).

25 Reference Example 156

To a solution of methyl 2-(4-methylphenyl)-7,8-dihydro-6H-cyclohepta[b]thiophene-5-carboxylate (803mg) in ethanol-tetrahydrofuran (5-10ml) was added 2N sodium hydroxide (2ml) at room temperature, and the mixture was
30 stirred for 5 days and concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (10ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced
35 pressure to precipitate crystals, which were collected by filtration and washed with diisopropylether to give 2-

(4-methylphenyl)-7,8-dihydro-6H-cyclohepta[b]thiophene-5-carboxylic acid (650mg) as pale yellow crystals.

m.p.250-251°C

¹H-NMR (200MHz, CDCl₃) δ 2.00-2.14 (2H, m), 2.36 (3H, s),
5 2.75-2.85 (2H, m), 3.07-3.16 (2H, m), 7.10 (1H, s), 7.18
(2H, d, J=8.0 Hz), 7.43 (2H, d, J=8.0 Hz), 7.72 (1H, s).
IR (KBr) 2910, 2831, 1670, 1614, 1423, 1287, 1242, 810cm⁻¹

Elemental Analysis for C₁₇H₁₄O₂S

Calcd. C, 71.80 ; H, 5.67 ; S, 11.28 :

10 Found. C, 71.74 ; H, 5.64 ; S, 11.06.

Reference Example 157

To a suspension of 5-bromonicotinic acid (5.0g) and
N-hydroxysuccinimide (4.27g) in acetonitrile (60ml) was
added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
15 hydrochloride (7.12g) at room temperature, and the mixture
was stirred for 30 minutes. To the reaction mixture were
added N,O-dimethyl-hydroxylamine hydrochloride (2.66g) and
triethylamine (10ml), and the mixture was stirred for 64
hours and concentrated under reduced pressure. To the
20 residue was added water, and the mixture was extracted with
ethyl acetate. The organic layer was washed with saturated
sodium chloride solution, dried with magnesium sulfate and
concentrated under reduced pressure. The residue was
separated and purified with column chromatography (ethyl
25 acetate/hexane=2:1) to give N-methyl-N-methoxy-5-bromo-
pyridine-3-carboxamide (3.71g) as pale yellow oil.

¹H-NMR (200MHz, CDCl₃) δ 3.40 (3H, s), 3.58 (3H, s), 8.19
(1H, dd, J=2.2, 1.8 Hz), 8.76 (1H, d, J=2.2 Hz), 8.88 (1H,
d, J=1.8 Hz).

30 IR (neat) 1647, 1412, 1381, 1221, 1099, 1020, 982, 897, 773,
739, 969, 667, 575, 461 cm⁻¹

Reference Example 158

Under argon atmosphere, a solution of N-methyl-N-
methoxy-5-bromopyridine-3-carboxamide (3.70g), 4-methyl-
35 phenyl borate (2.26g) and potassium carbonate (4.17g) in
toluene-ethanol-water (100-10-10ml) was stirred at room

temperature for 1 hour. To the reaction mixture was added tetrakis(triphenylphosphine)palladium (0.52g), and the mixture was refluxed for 16 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:2→1:1) to give N-methyl-N-methoxy-5-(4-methylphenyl)pyridine-3-carboxamide (3.97g) as yellow oil.

¹H-NMR (200MHz, CDCl₃) δ 2.42 (3H, s), 3.42 (3H, s), 3.60 (3H, s), 7.30 (2H, d, J=8.3 Hz), 7.51 (2H, d, J=8.3 Hz), 8.20 (1H, t, J=2.1 Hz), 8.89-8.81 (2H, m).
IR (neat) 1647, 1431, 1379, 1203, 982, 818, 743, 540, 426 cm⁻¹

Reference Example 159

Under nitrogen atmosphere, to a solution of N-methyl-N-methoxy-5-(4-methylphenyl)pyridine-3-carboxamide (3.95g) in tetrahydrofuran (30ml) was dropwise added diisobutylaluminum hydride (1.01M toluene solution) (30ml) at -78°C, and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added 1N hydrochloric acid to stop the reaction. To the mixture was added ethyl acetate, and the mixture was made alkaline with 1N sodium hydroxide. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:2→1:1) to give 5-(4-methylphenyl)pyridine-3-carboxyaldehyde (1.82g) as colorless crystals.

m.p. 60-61°C

¹H-NMR (200MHz, CDCl₃) δ 2.43 (3H, s), 7.33 (2H, d, J=7.8 Hz), 7.54 (2H, d, J=7.8 Hz), 8.33 (1H, dd, J=2.2, 2.0 Hz), 9.03 (1H, d, J=2.0 Hz), 9.07 (1H, d, J=2.2 Hz), 10.19 (1H, s).

IR (KBr) 1701, 1186, 818, 725, 806 cm^{-1}

Elemental Analysis for $\text{C}_{13}\text{H}_{11}\text{NO}$

Calcd. C, 79.17 ; H, 5.62 ; N, 7.10 :

Found. C, 79.24 ; H, 5.64 ; N, 7.01.

5 Reference Example 160

A solution of 5-(4-methylphenyl)pyridine-3-carboxy-
aldehyde (1.82g) and methyl (triphenylphosphoranilidene)-
acetate (3.46g) in toluene (20ml) was refluxed under
nitrogen atmosphere for 4 hours and cooled. To the mixture
10 was added water, and the mixture was extracted with ethyl
acetate. The organic layer was washed with saturated sodium
chloride solution, dried with magnesium sulfate and
concentrated under reduced pressure. The residue was
separated and purified with column chromatography (ethyl
15 acetate/hexane=1:2→1:1) to give methyl (E)-3-[5-(4-
methylphenyl)pyridin-3-yl]acrylate (2.34g) as colorless
crystals.

m.p. 141-144°C

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 2.43 (3H, s), 3.84 (3H, s), 6.59
20 (1H, d, $J=16.0$ Hz), 7.32 (2H, d, $J=7.9$ Hz), 7.50 (2H, d,
 $J=7.9$ Hz), 7.76 (1H, d, $J=16.0$ Hz), 7.98 (1H, dd, $J=2.2$,
2.0 Hz), 8.70 (1H, d, $J=2.0$ Hz), 8.82 (1H, d, $J=2.2$ Hz).
IR (KBr) 1718, 1639, 1431, 1335, 1196, 1176, 995, 816 cm^{-1}

Elemental Analysis for $\text{C}_{16}\text{H}_{15}\text{NO}_2$

25 Calcd. C, 75.87 ; H, 5.97 ; N, 5.53 :

Found. C, 75.82 ; H, 5.86 ; N, 5.47.

Reference Example 161

To a solution of methyl (E)-3-[5-(4-methylphenyl)-
pyridin-3-yl]acrylate (2.25g) in tetrahydrofuran (20ml)
30 was added 1N sodium hydroxide (11ml) at room temperature,
and the mixture was stirred for 5 days. To the reaction
mixture was added 1N hydrochloric acid (12ml), and the
mixture was concentrated under reduced pressure to
precipitate crystals, which were collected by filtration
35 and washed with water and diethylether to give (E)-3-
[5-(4-methylphenyl)pyridin-3-yl]acrylic acid (1.92g) as

colorless crystals.

m.p. 208-211°C

¹H-NMR (200MHz, DMSO-d₆) δ 2.37 (3H, s), 6.85 (1H, d, J=16.2 Hz), 7.33 (2H, d, J=8.6 Hz), 7.66-7.74 (3H, m), 8.40-8.45 (1H, m), 8.81 (1H, d, J=1.8 Hz), 8.89 (1H, d, J=2.2 Hz).

IR (KBr) 3030, 1672, 1635, 1435, 1331, 1302, 987, 820 cm⁻¹

Elemental Analysis for C₁₅H₁₃NO₂

Calcd. C, 75.30 ; H, 5.48 ; N, 5.85 ;

Found. C, 74.99 ; H, 5.39 ; N, 5.94.

10 Reference Example 162

To DMF (7.18ml) was dropwise added phosphoryl chloride (8.64ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added methyl acetoacetate (10ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. The mixture was cooled to 0°C, and to the mixture was added 4-bromoaniline (16.78g), and the mixture was stirred at 90°C for 4 hours. To the reaction mixture was added chloroform, and the mixture was neutralized with 8N sodium hydroxide. The organic layer was washed with water and saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:2) and was recrystallized from ethyl acetate-hexane to give methyl 6-bromo-2-methylquinoline-3-carboxylate (6.02g) as pale yellow crystals.

m.p. 150-151°C

¹H-NMR (200MHz, CDCl₃) δ 2.97 (3H, s), 3.99 (3H, s), 7.84 (1H, dd, J=9.0, 2.0 Hz), 7.92 (1H, d, J=9.0 Hz), 8.02 (1H, d, J=2.0 Hz), 8.65 (1H, s).

IR (KBr) 1726, 1423, 1396, 1277, 1238, 1219, 1134, 1074, 829 cm⁻¹

Elemental Analysis for C₁₂H₁₀NO₂Br

Calcd. C, 51.45 ; H, 3.60 ; N, 5.00 ;

35 Found. C, 51.57 ; H, 3.55 ; N, 5.17.

Reference Example 163

Under argon atmosphere, a solution of methyl 6-bromo-2-methylquinoline-3-carboxylate (1.22g), 4-methylphenyl borate (0.65g) and potassium carbonate (1.18g) in toluene-ethanol-water (40-4-4ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis-triphenylphosphinepalladium (0.15g), and the mixture was refluxed for 18 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:1) to give methyl 6-(4-methylphenyl)-2-methylquinoline-3-carboxylate (1.27g) as colorless crystals.

m.p. 84-87°C
¹H-NMR (200MHz, CDCl₃) δ 2.43 (3H, s), 3.01 (3H, s), 4.00 (3H, s), 7.32 (2H, d, J=8.0 Hz), 7.61 (2H, d, J=8.0 Hz), 8.01-8.12 (3H, m), 8.79 (1H, s).

IR (KBr) 1732, 1440, 1277, 1213, 1068, 814 cm⁻¹

Elemental Analysis for C₁₉H₁₇NO₂

Calcd. C, 78.33 ; H, 5.88 ; N, 4.81 :

Found. C, 77.98 ; H, 6.02 ; N, 4.75.

Reference Example 164

To a solution of methyl 6-(4-methylphenyl)-2-methylquinoline-3-carboxylate (0.99g) in tetrahydrofuran-ethanol (5-5ml) was added 2N sodium hydroxide (2ml) at room temperature, and the mixture was stirred for 2 days. To the reaction mixture was added 1N hydrochloric acid (4ml), and the mixture was concentrated under reduced pressure to precipitate crystals, which were collected by filtration and washed with ethanol and diethylether to give 6-(4-methylphenyl)-2-methylquinoline-3-carboxylic acid (648mg) as colorless crystals.

m.p. 273°C (dec.)

¹H-NMR (200MHz, DMSO-d₆) δ 2.38 (3H, s), 2.89 (3H, s), 7.34 (2H, d, J=8.3 Hz), 7.74 (2H, d, J=8.3 Hz), 8.02 (1H, d, J=8.8 Hz), 8.15 (1H, dd, J=8.8, 2.1 Hz), 8.37 (1H, d, J=2.1 Hz),

8.90 (1H, s).

IR (KBr) 2918, 1703, 1570, 1495, 1257, 1227, 1180, 1151, 1065, 812, 770 cm^{-1}

Elemental Analysis for $\text{C}_{18}\text{H}_{15}\text{NO}_2$

5 Calcd. C, 77.96 ; H, 5.45 ; N, 5.05 ;

Found. C, 77.74 ; H, 5.34 ; N, 5.12.

Reference Example 165

Under argon atmosphere, a solution of ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (1.0g), 4-methylthiophenyl borate (622mg) and potassium carbonate (0.93g) in toluene-ethanol-water (30-3-3ml) was stirred at room temperature for 1 hour. To the reaction mixture was added tetrakis(triphenyl-phosphine)palladium (117mg), and the mixture was refluxed for 16 hours. To the reaction mixture was added tetrakis(triphenyl-phosphine)palladium (0.13g), and the mixture was refluxed for 24 hours and cooled to room temperature. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate/hexane=1:10) to give ethyl 7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (442mg) as colorless crystals.

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.36 (3H, t, $J=7.0$ Hz), 2.52 (3H, s), 3.00 (2H, t, $J=4.8$ Hz), 4.29 (2H, q, $J=7.0$ Hz), 4.30 (2H, t, $J=4.8$ Hz), 7.04 (1H, d, $J=8.4$ Hz), 7.32 (2H, d, $J=8.8$ Hz), 7.42-7.54 (4H, m), 7.65 (1H, br s).

IR (KBr) 1705, 1489, 1302, 1250, 1230, 1200, 1090, 1063, 1011, 813 cm^{-1}

30 Reference Example 166

To a solution of ethyl 7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (132mg) in ethanol-tetrahydrofuran (5ml-5ml) was added 1N sodium hydroxide (1.0ml) at room temperature, and the mixture was stirred for 20 hours and concentrated under reduced pressure. To the residue was added 1N hydrochloric acid (2ml) and the

mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The resulting crystal was collected by filtration to give 7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (113mg) as colorless crystals.

¹H-NMR (200MHz, DMSO-d₆) δ 2.51 (3H, s.), 2.89 (2H, t, J=4.4 Hz), 4.25 (2H, t, J=4.4 Hz), 7.04 (1H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.58 (1H, dd, J=8.4, 2.4 Hz), 7.61-7.70 (3H, m), 7.80 (1H, d, J=2.4 Hz).

IR (KBr) 2974, 1689, 1493, 1263, 1213, 1169, 1020, 833 cm⁻¹

Reference Example 167

To a solution of 4-nitrobenzylalcohol (50 g, 0.326 mol) in ethyl acetate (EtOAc) (200 ml) were added 3,4-dihydropyran (35.7 ml, 0.392 mol) and CSA (camphor sulfonic acid) (379 mg, 1.63 mmol) under stirring at room temperature, and the mixture was stirred at room temperature for 1 hour. After the reaction completed, the reaction mixture was neutralized with saturated NaHCO₃ solution and separated ethyl acetate layer was dried with MgSO₄ and concentrated under reduced pressure. The residue was purified with silica gel column chromatography to give 4-(2-tetrahydropyranyloxymethyl)nitrobenzene (74.5 g, 96%) as syrup.

¹H-NMR (200 MHz, CDCl₃) δ: 1.55-2.05 (6H, m), 3.51-3.62 (1H, m), 3.83-3.94 (1H, m), 4.61 (1H, d, J=13.6Hz), 4.74 (1H, t, J=3.2Hz), 4.93 (1H, d, J=13.4Hz), 7.51-7.56 (2H, d, J=8.8Hz), 8.18-8.24 (2H, m).

Reference Example 168

To a solution of 4-(2-tetrahydropyranyloxymethyl)-nitrobenzene (59.7 g, 0.256 mol) in ethanol (EtOH) (300 ml) was added under nitrogen atmosphere at room temperature 10% Pd/C (5.97 g), and catalytic hydrogenation was carried out. The mixture was stirred at room temperature for 24 hours. After the reaction completed, the catalyst was filtered off, and the organic layer was concentrated under reduced

pressure. The residue was purified with silica gel column chromatography to give 4-(2-tetrahydropyranyloxymethyl)-aniline (39.7 g, 76%) as syrup.

¹H-NMR (200 MHz, CDCl₃) δ : 1.45-1.95 (6H, m), 3.00-3.60 (3H, br m), 3.87-4.14 (1H, m), 4.39 (1H, d, J=11.4Hz), 4.68 (1H, d, J=11.4Hz), 4.71 (1H, m), 6.65-6.69 (2H, m), 7.15-7.19 (2H, m).

Reference Example 169

To a solution of 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (35.0 g, 0.126 mol) in tetrahydrofuran (THF) (280 ml) were added (COCl)₂ (21.9 ml, 0.251 mol) and DMF (0.7 ml) at 0°C. Under nitrogen atmosphere, the mixture was stirred at room temperature for 4 hours. After the reaction completed, the solvent was evaporated, and to the residue was added THF (315 ml). To a solution of the acid chloride was added a solution of 4-(2-tetrahydropyranyloxymethyl)aniline (28.1 g, 0.138 mol) and triethylamine (Et₃N) (26.3 ml, 0.189 mol) in THF (105 ml) at 0°C, and the mixture was stirred under nitrogen atmosphere, at room temperature for 2 hours. After the reaction completed, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution and dried with MgSO₄. The solvent was evaporated and the residue was dissolved in methanol (MeOH) (470 ml). To the mixture was dropwise added 6N HCl (5.9 ml) at room temperature, and the mixture was stirred for 1 hour. After the reaction completed, the mixture was neutralized with saturated NaHCO₃ solution, and the solvent was removed. The residue was washed with water and then acetone/isopropylether (10:1; 60 ml), and the resulting precipitate was filtered, which was dissolved in THF. The mixture was dried with MgSO₄, and the solvent was evaporated. The resulting powder was washed twice with hexane:ethyl acetate (10:1; 50 ml) to give N-(4-hydroxymethylphenyl)-3-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-6-carboxamide (26.8 g).

56%) as white powder.

¹H-NMR (200 MHz, CDCl₃) δ: 2.10-2.22 (2H, m), 2.39 (3H, s),
2.71 (2H, br t, J=6.4), 2.84-2.91 (2H, m), 4.67 (2H, s),
7.20-7.26 (2H, m), 7.33-7.51 (7H, m), 7.61 (2H, d, J=8.4),
5 7.71 (1H, br s).

Reference Example 170

To a solution of N-(4-hydroxymethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (10.0 g, 26.1 mmol) and pyridine (0.1 ml) in
10 chloroform (150 ml) was dropwise added a solution of thionyl chloride (3.4 ml, 39.2 mmol) in chloroform (90 ml), and the mixture was stirred under nitrogen atmosphere at room temperature for 17 hours. After the reaction completed, water was added to the mixture, and the mixture was extracted
15 with chloroform. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the resulting powder was washed with hexane to give N-(4-chloromethylphenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (10.2 g, 97%) as
20 colorless powder.

¹H-NMR (200 MHz, CDCl₃) δ: 2.05-2.21 (2H, m), 2.40 (3H, s),
2.71 (2H, br t, J=6.4), 2.84-2.91 (2H, m), 4.58 (2H, s),
7.20-7.27 (2H, m), 7.35-7.52 (7H, m), 7.59-7.65 (2H, m),
25 7.71 (1H, br s).

Anal. for C₂₆H₂₄NOCl·0.25H₂O:

Calcd: C; 76.83, H; 6.08, N; 3.45.

Found: C; 76.55, H; 6.00, N; 3.53.

Reference Example 171

30 To a solution of tetrahydro-4H-pyran-4-one (60 g, 0.6 mol) and water (5 ml) in DMF (70 ml, 0.90 mol) was added formic acid (46 ml, 1.2 mol), and the mixture was stirred at 140°C for 23 hours. After the reaction completed, reflux apparatus was changed to evaporation apparatus, crude amine
35 was obtained by evaporation (74.6 g).
b.p. 117 - 123 °C (27 mm).

To an aqueous solution (100 ml) of the crude amine (30 g) was dropwise added 6N HCl (5 drops), and the mixture was washed twice with dichloromethane. The aqueous layer was adjusted to pH 11 with sodium hydroxide. To the mixture was added NaCl, and the mixture was extracted with dichloromethane three times. The organic layer was dried with potassium carbonate, and the solvent was evaporated. The residue was purified with evaporation to give N,N-dimethyl-N-tetrahydropyran-4-ylamine (10.4 g, 29%) as colorless oil.

b.p. 75-82 °C (29 mm).

¹H-NMR (200 MHz, CDCl₃) δ: 1.40-1.82 (4H, m), 2.28 (6H, s), 2.25-2.40 (1H, m), 3.37 (2H, ddd, J=11.8, 11.8 and 2.2), 3.97-4.05 (2H, m).

Reference Example 172

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.6 g, 2.1 mmol) in tetrahydrofuran (10 ml) were added oxalyl chloride (0.33 ml, 4.3 mmol) and N,N-dimethylformamide (1 drop) at 0°C, and the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (6 ml). To the mixture was dropwise added 4-(tert-butyldimethylsilyloxymethyl)aniline (0.56 g, 2.4 mmol) and triethylamine (0.36 ml, 2.6 mmol) in tetrahydrofuran (2 ml) at 0°C, and the mixture was stirred at room temperature for 16 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated, and the residue was subjected to silica gel column chromatography. Crude amide (1.1 g) was obtained from fractions of hexane:ethyl acetate=5:1. This product was dissolved in acetone (8 ml), and to the mixture was dropwise added 6N hydrochloric acid. The mixture was stirred for 1 hour. To the mixture were added 1% sodium hydrogen carbonate (100 ml) and diisopropylether (100 ml),

and precipitate was filtered, which were dissolved in acetone. The mixture was dried with magnesium sulfate, and the solvent was evaporated. The resulting powder was recrystallized from acetone-diisopropyl-ether to give

5 N-(4-hydroxymethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.87 g) as colorless crystals.

¹H-NMR (CDCl₃) δ: 2.39 (3H, s), 3.08 (2H, br t, J=4.4), 4.36 (2H, t, J=4.4), 4.68 (2H, s), 7.06 (2H, d, J=8.4), 7.18-7.61

10 (10H, m), 7.24 (2H, d, J=8.4).

Anal. for C₂₅H₂₃NO₃:

Calcd: C; 77.90, H; 6.01, N; 3.63.

Found: C; 77.91, H; 6.10, N; 3.55.

Reference Example 173

15 To a solution of N-(4-hydroxymethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (412 mg, 1.07 mmol) and pyridine (1 drop) in chloroform (5 ml) was dropwise added thionyl chloride (0.14 ml, 1.61 mmol), and the mixture was stirred for 2 hours. The mixture was

20 diluted with water and extracted with chloroform. The extract was washed with saturated sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated, and the resulting powder was washed with

25 hexane-ethyl acetate (1:1) to give N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (380 mg, 88%) as colorless powder.

m.p. 164°C

¹H-NMR (CDCl₃) δ: 3.29 (3H, s), 3.07 (2H, t, J=4.8), 4.36 (2H, t, J=4.8), 4.59 (2H, s), 7.05 (1H, d, J=8.2), 7.22-7.26 (2H,

30 m), 7.36-7.52 (6H, m), 7.57-7.62 (3H, m).

Anal. for C₂₅H₂₂NO₂Cl:

Calcd: C; 74.34, H; 5.49, N; 3.47.

Found: C; 74.00, H; 5.42, N; 3.29.

Reference Example 174

35 To a suspension of 1,4-cyclohexanedione monoethylene-ketal (3.82 g, 24.6 mmol) and dimethylamine hydrochloride

(2.00 g, 24.6 mmol) in 1,2-dichloroethane (50 ml) were dropwise added triethylamine (4.2 ml, 29.6 mmol) and DBU (1,8-diazabicyclo-[5.4.0]-7-undecene) (4.4 ml), and the mixture was stirred for 10 minutes. To the mixture was added triacetoxymethylborohydride (7.68 g, 34.4 mmol), and the mixture was stirred for 4.5 hours. Precipitate was filtered off, and the filtrate was concentrated to give crude product (6.34 g), which was dissolved in water (10 ml). To the mixture was dropwise added concentrated hydro-chloric acid (6 ml), and the mixture was stirred for 48 hours. The reaction mixture was diluted with water and washed twice with ether. The aqueous layer was made basic with sodium hydroxide and extracted with ether twice. The extract was washed with saturated sodium chloride solution, dried with potassium carbonate and purified by evaporation to give 4-dimethylaminocyclohexanone (0.59 g, 17%).

b.p. 142-5°C

¹H-NMR (CDCl₃) δ: 1.69-2.13 (4H, m), 2.32 (6H, s), 2.20-2.41 (2H, m), 2.44-2.64 (3H, m).

Reference Example 175

To a solution of 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (2.38 g) in THF (50 ml) were added oxalyl chloride (1.4 ml) and DMF (2 drops) at room temperature, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (50 ml). To the mixture was dropwise added a solution of triethylamine (2.1 ml) and 4-aminobenzyloxy-tert-butyldimethylsilane (2.00 g) in THF (10 ml) at 0°C, and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified with column chromatography (ethyl acetate /hexane =1:4) to give pale yellow crystals (3.99 g), which were

dissolved in acetone (50 ml). To the mixture was added 6N hydrochloric acid (1.3 ml) at room temperature, and the mixture was stirred for 1 hour. To the reaction mixture were added 5% sodium hydrogen carbonate solution (15 ml) and diisopropylether (100 ml). Precipitate was collected by filtration and washed with water and diisopropylether. The resulting solid was dissolved in THF, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from THF to give 7-(4-ethoxyphenyl)-N-(4-hydroxymethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (2.65 g) as colorless crystals.

m.p. 208-210 °C

¹H-NMR (200MHz, DMSO-d₆) δ: 1.35 (3H, t, J=7.0 Hz), 2.93-3.03 (2H, m), 4.06 (2H, q, J=7.0 Hz), 4.45 (2H, br s), 5.01-5.18 (1H, m), 6.98-7.05 (3H, m), 7.25-7.34 (3H, m), 7.49-7.71 (6H, m), 9.92 (1H, s).

IR (KBr) ν: 3363, 3290, 1659, 1612, 1525, 1493, 1242, 1227, 825 cm⁻¹

Anal. for C₂₆H₂₅NO₄

Calcd: C, 75.16 ; H, 6.06 ; N, 3.37

Found: C, 75.16 ; H, 6.08 ; N, 3.31.

Reference Example 176

To a suspension of 7-(4-ethoxyphenyl)-N-(4-hydroxymethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (2.55 g) and pyridine (2 drops) in chloroform (50 ml) was added thionyl chloride (0.8 ml) at room temperature, and the mixture was stirred for 20 hours. To the reaction mixture was added water and then THF, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated under reduced pressure to give solid, which was dissolved in THF and ethyl acetate. The mixture was concentrated under reduced pressure to give crystals, which were collected by filtration and washed with diisopropylether to give N-(4-chloromethylphenyl)-7-(4-

ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(2.42 g) as colorless crystals.

m.p. 187-189 °C

¹H-NMR (200MHz, DMSO-d₆) δ: 1.35 (3H, t, J=7.0 Hz), 2.93-
3.04 (2H, m), 4.06 (2H, q, J=7.0 Hz), 4.23-4.34 (2H, m),
4.74 (2H, s), 6.98-7.06 (3H, m), 7.35-7.42 (3H, m), 7.52
(1H, dd, J=8.4, 2.2 Hz), 7.59 (2H, d, J=8.8 Hz), 7.70-7.74
(3H, m), 10.04 (1H, s).

IR (KBr) ν: 3400, 1659, 1610, 1525, 1493, 1242, 1047, 822
cm⁻¹

Anal. for C₂₆H₂₄NO₃Cl

Calcd: C, 71.97 ; H, 5.57 ; N, 3.23

Found: C, 71.96 ; H, 5.54 ; N, 3.04.

Working Example 227 (Production of Compound 227)

To solution of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-
N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-
dihydro-1-benzoxepine-4-carboxamide (111 mg) in DMF (5 ml)
was added methyl iodide (0.04 ml) at room temperature, and
the mixture was stirred for 8 hours. Under reduced pressure,
the mixture was concentrated, and to the residue was added
ethyl acetate to precipitate solid, which was collected by
filtration and recrystallized from ethanol-ethyl acetate
to give dimethyl-[4-N-[7-(4-ethoxyphenyl)-2,3-dihydro-
1-benzoxepin-4-carbonyl]aminobenzyl]-4-tetrahydro-
pyranilammonium iodide (97 mg) as pale yellow crystals.
m.p. 152-158 °C

¹H-NMR (200MHz, CDCl₃) δ: 1.41 (3H, t, J=7.0 Hz), 1.68-1.98
(2H, m), 2.10-2.26 (2H, m), 2.94 (6H, s), 2.98-3.08 (2H,
m), 3.35-3.59 (3H, m), 3.96-4.16 (2H, m), 4.03 (2H, q, J=7.0
Hz), 4.19-4.31 (2H, m), 4.84 (2H, s), 6.91 (2H, d, J=8.8
Hz), 6.97 (1H, d, J=8.4 Hz), 7.38 (1H, dd, J=8.4, 2.2 Hz),
7.44-7.57 (5H, m), 7.69 (1H, d, J=2.2 Hz), 7.80 (2H, d, J=8.4
Hz), 8.01 (1H, s).

IR (KBr) ν: 3440, 1657, 1605, 1520, 1491, 1317, 1240 cm⁻¹

Anal. for C₃₃H₃₉N₂O₄I·1.0H₂O

Calcd: C, 58.93 ; H, 6.14 ; N, 4.16

Found: C, 58.86 ; H, 6.18 ; N, 4.19.

Working Example 228 (Production of Compound 228)

To a solution of 7-(4-ethylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (125 mg) in DMF (5 ml) was added methyl iodide (0.04 ml) at room temperature, and the mixture was stirred for 20 hours. Under reduced pressure, the mixture was concentrated, and to the residue was added ethyl acetate to precipitate solid, which was collected by filtration and recrystallized from acetone-diethylether→ethanol-diethylether) to give dimethyl-[4-N-[7-(4-ethylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl]aminobenzyl]-4-tetrahydropyranylammonium iodide (68 mg) as pale yellow crystals.

m.p. 156-160 °C

¹H-NMR (200MHz, CDCl₃) δ: 1.25 (3H, t, J=7.6 Hz), 1.69-1.93 (2H, m), 2.13-2.28 (2H, m), 2.66 (2H, q, J=7.6 Hz), 2.95 (6H, s), 3.00-3.09 (2H, m), 3.39-3.56 (2H, m), 4.02-4.34 (5H, m), 4.86 (2H, s), 6.99 (1H, d, J=8.4 Hz), 7.18-7.28 (3H, m), 7.39-7.56 (5H, m), 7.69-7.73 (1H, m), 7.79 (2H, d, J=8.8 Hz), 8.78 (1H, s).

IR (KBr) ν: 3429, 1657, 1301, 1520, 1491, 1412, 1319, 1244, 827 cm⁻¹

Anal. for C₃₃H₃₉N₂O₃I·1.0H₂O

Calcd: C, 60.37 ; H, 6.29 ; N, 4.27

Found: C, 60.40 ; H, 6.24 ; N, 4.10.

Working Example 229 (Production of Compound 229)

To a solution of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (113.6 mg) in DMF (5 ml) was added methyl iodide (0.04 ml) at room temperature, and the mixture was stirred for 24 hours. Under reduced pressure, the mixture was concentrated, and to the residue was added ethyl acetate to precipitate solid, which was collected by filtration and recrystallized from acetone-diethylether→ethanol-diethyl-ether) to give dimethyl-

[4-N-[7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl]aminobenzyl]-4-tetrahydropyranylammonium iodide (99 mg) as pale yellow crystals. m.p. 213 °C (dec.)

- 5 ¹H-NMR (200MHz, DMSO-d₆) δ: 1.42-1.66 (2H, m), 1.75-1.88 (2H, m), 2.55 (6H, s), 2.62-2.72 (2H, m), 2.94-3.35 (3H, m), 3.68-3.81 (2H, m), 3.96-4.08 (2H, m), 4.13 (2H, s), 6.80 (1H, d, J=8.8 Hz), 7.05 (1H, s), 7.21 (2H, d, J=8.4 Hz), 7.34-7.40 (1H, m), 7.44-7.63 (7H, m), 9.89 (1H, s).
- 10 IR (KBr) ν: 3277, 1649, 1510, 1520, 1491, 1325, 1255, 1120, 843 cm⁻¹

Anal. for C₃₂H₃₄N₂O₃F₃I·0.2H₂O

Calcd: C, 56.35 ; H, 5.08 ; N, 4.11

Found: C, 56.21 ; H, 5.16 ; N, 4.11.

- 15 Reference Example 177

In 1,2-dichloroethane(400 ml) was suspended p-nitrobenzylamine hydrochloride (30.8 g), 1,4-cyclohexane-dione monoethyleneketal (25.4 g) and triethylamine (23 ml), and to the suspension was added sodium triacetoxo boron hydride (50.9 g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature for 2.5 hours. Under ice-cooling, 37% formalin (14.6 ml) and sodium triacetoxo boron hydride (50.9 g) were added to the mixture. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The mixture was neutralized with sodium hydrogen carbonate and extracted with 1,2-dichloroethane. The organic layer was washed with sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow solid (47.5 g), 44 g of which was dissolved in (660 ml). To the mixture was added reduced iron (32 g) little by little, and the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitate was filtered off, and the filtrate was made alkaline with potassium carbonate and extracted with ethyl acetate. The organic layer was

washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/triethylamine/methanol) to give 4-((N-(4,4-ethylenedioxcyclohexyl)-N-methyl)aminomethyl)aniline (34.1 g) as brown oil.

¹H-NMR(CDCl₃) δ: 1.36-1.93 (8H, m), 2.17 (3H, s), 2.43-2.57 (1H, m), 3.46 (2H, s), 3.60 (2H, br), 3.94 (4H, s), 6.64 (2H, d, J=8.4Hz), 7.09 (2H, d, J=8.4Hz).
IR(neat) ν: 2946, 1615cm⁻¹.

Working Example 230 (Production of Compound 230)

In dichloromethane (400 ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (17.0 g), and to the suspension were added oxalyl chloride (10.3 ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (300 ml), and the mixture was dropwise added to a solution of 4-((N-(4,4-ethylenedioxcyclohexyl)-N-methyl)aminomethyl)-aniline (16.75 g) and triethylamine (25 ml) in tetrahydrofuran (200 ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate to give N-(4-((N-(4,4-ethylenedioxcyclohexyl)-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (17.1 g) as colorless crystals.
mp 192-193°C.

¹H-NMR(CDCl₃) δ: 1.48-1.86 (8H, m), 2.20 (3H, s), 2.39 (3H,

s), 2.45-2.60 (1H, m), 3.08 (2H, t, J=4.5Hz), 3.56 (2H, s), 3.95 (4H, s), 4.36 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.4Hz), 7.23-7.33 (4H, m), 7.44-7.56 (7H, m).

IR(KBr) ν : 2948, 1651 cm^{-1} .

5 Anal. for $\text{C}_{34}\text{H}_{38}\text{N}_2\text{O}_4$:

Calcd: C, 75.81; H, 7.11; N, 5.20.

Found: C, 75.51; H, 6.99; N, 5.29.

Working Example 231 (Production of Compound 231)

In acetic acid (100 ml) and 1N hydrochloric acid (200
10 ml) was dissolved N-(4-((N-(4,4-ethylenedioxcyclohexyl)-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (17.1 g), and the mixture was stirred at 100°C for 1.5 hours and concentrated. The residue was neutralized with 1N sodium hydroxide and
15 extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-methanol to give
20 N-(4-((N-(4-oxocyclohexyl)-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (12 g) as colorless crystals.
mp 149-150°C.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.78-2.13 (4H, m), 2.23 (3H, s), 2.25-2.35
25 (2H, m), 2.39 (3H, s), 2.45-2.57 (2H, m), 2.84-2.94 (1H, m), 3.08 (2H, t, J=4.4Hz), 3.59 (2H, s), 4.35 (2H, t, J=4.4Hz), 7.06 (1H, d, J=8.0Hz), 7.22-7.34 (4H, m), 7.43-7.57 (6H, m), 7.65 (1H, s).

IR(KBr) ν : 2946, 1713 cm^{-1} .

30 Anal. for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_3$

Calcd: C, 77.70; H, 6.93; N, 5.66.

Found: C, 77.45; H, 6.78; N, 5.65.

Reference Example 178

To a mixture of methyl 2-bromo-6,7-dihydro-5H-
35 benzocycloheptene-8-carboxylate (0.5 g), 4-(1-pyrrolidinyl)phenyl borate(0.37 g), 1M potassium carbonate

(6 ml) and ethanol(6 ml) was added toluene (50 ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.08 g), and the mixture was refluxed for 6 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give colorless crystals (0.48 g), which were dissolved in 1N sodium hydroxide (15 ml), methanol (50 ml) and tetrahydrofuran (50 ml). The mixture was stirred at room temperature overnight, concentrated and neutralized with hydrochloric acid to precipitate 2-(4-(1-pyrrolidinyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.46 g) as pale yellow crystals.

mp 242-243°C(dec.).

¹H-NMR(DMSO-d₆) δ: 1.93-2.00 (6H, m), 2.56 (2H, t, J=5.8Hz), 2.76-2.82 (2H, m), 3.23-3.35 (4H, m), 6.60 (2H, d, J=8.8Hz), 7.20 (1H, d, J=8.2Hz), 7.44 (1H, dd, J=1.0, 8.2Hz), 7.53 (2H, d, J=8.8Hz), 7.56 (1H, d, J=1.0Hz), 7.69 (1H, s).

Anal. for C₂₂H₂₃NO₂·0.1H₂O:

Calcd: C, 78.82; H, 6.98; N, 4.18.

Found: C, 78.92; H, 6.95; N, 4.15.

Working Example 232 (Production of Compound 232)

To a solution of 2-(4-(1-pyrrolidinyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.45 g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.33 g) and 1-hydroxybenzotriazole (0.18 g) in dimethylformamide (20 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.39 g) under ice-cooling. Under nitrogen atmosphere, the reaction mixture was cooled to room temperature, and to the mixture were added 4-dimethylaminopyridine (catalytic amount) and triethylamine (0.56 ml). The mixture was stirred overnight,

poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 2-(4-(1-pyrrolidinyl)phenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methyl)aminomethyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.28 g) as colorless crystals.

mp 124-125°C.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.66-1.77 (4H, m), 1.99-2.06 (4H, m), 2.11-2.18 (2H, m), 2.21 (3H, s), 2.55-2.75 (3H, m), 2.84-2.90 (2H, m), 3.30-3.44 (6H, m), 3.58 (2H, s), 4.00-4.14 (2H, m), 6.64 (2H, d, $J=9.0\text{Hz}$), 7.19 (1H, d, $J=8.0\text{Hz}$), 7.31 (2H, d, $J=8.5\text{Hz}$), 7.39-7.51 (4H, m), 7.57 (2H, d, $J=8.5\text{Hz}$), 7.64 (1H, s).

IR(KBr) ν : 2946, 2843, 1651, 1611 cm^{-1} .

Anal. for $\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_2 \cdot 0.2\text{H}_2\text{O}$

Calcd: C, 77.95; H, 7.74; N, 7.79.

Found: C, 77.76; H, 7.59; N, 7.79.

Reference Example 179

In 1,2-dichloroethane (50 ml) were dissolved p-nitrobenzaldehyde (5 g) and 3-amino-1-propanol (2.5 g), and to the mixture was added sodium triacetoxymethylborohydride (9.8 g) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature for 5 hours. Under ice-cooling, to the mixture was added 37% formalin (3 ml) and sodium triacetoxymethylborohydride (9.8 g). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. To the mixture was added water, and the mixture was concentrated, neutralized with aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure,

the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give yellow oil (5.0 g), 2.5g of which was dissolved in ethanol(50 ml) and catalytic hydrogenation was carried out with 5% palladium on carbon (0.2 g) for 1.5 hours. The catalyst was filtered off, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give 4-((N-3-hydroxypropyl-N-methyl)aminomethyl)-aniline (1.5 g) as pale yellow oil.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.67-1.78 (2H, m), 2.21 (3H, s), 2.62 (2H, t, $J=5.5\text{Hz}$), 3.41 (2H, s), 3.65 (2H, br), 3.77 (2H, t, $J=5.1\text{Hz}$), 6.65 (2H, d, $J=8.4\text{Hz}$), 7.07 (2H, d, $J=8.4\text{Hz}$). IR(neat) ν : 3347, 2948, 2799, 1615 cm^{-1} .

Working Example 233 (Production of Compound 233)

In dichloromethane (5 ml) was suspended 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.3 g), and to the suspension were added oxalyl chloride (0.28 ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 1.5 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 ml), and the mixture was dropwise added to a solution of 4-((N-3-hydroxypropyl-N-methyl)aminomethyl)aniline (0.23 g) and triethylamine (0.45 ml) in tetrahydrofuran (15 ml) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-3-hydroxypropyl-N-methyl)aminomethyl)phenyl)-2-(4-

methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.32 g) as colorless crystals.

mp 139-140°C.

¹H-NMR(CDCl₃) δ: 1.72-1.81 (2H, m), 2.13-2.19 (2H, m), 2.25 (3H, s), 2.40 (3H, s), 2.63-2.75 (4H, m), 2.86-2.92 (2H, m), 3.53 (2H, s), 3.79 (2H, t, J=5.4Hz), 7.21-7.32 (3H, m), 7.42-7.52 (6H, m), 7.58 (2H, d, J=8.4Hz), 7.66 (1H, s).

IR(KBr) ν: 2936, 1651cm⁻¹.

Anal. for C₃₀H₃₄N₂O₂·0.5H₂O:

10 Calcd: C, 77.72; H, 7.61; N, 6.04.

Found: C, 77.94; H, 7.62; N, 6.15.

Working Example 234 (Production of Compound 234)

In dichloromethane(12 ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.4 g), and to the suspension were added oxalyl chloride (0.37 ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 ml), and the mixture was dropwise added to a solution of 4-((N-3-hydroxy-propyl-N-methyl)aminomethyl)aniline (0.33 g) and tri-ethylamine (0.6 ml) in tetrahydrofuran(15 ml) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-3-hydroxypropyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.39 g) as colorless crystals. mp 119-120°C.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.68-1.80 (2H, m), 2.24 (3H, s), 2.39 (3H, s), 2.65 (2H, t, $J=5.8\text{Hz}$), 3.07 (2H, t, $J=4.6\text{Hz}$), 3.52 (2H, s), 3.77 (2H, t, $J=5.2\text{Hz}$), 4.35 (2H, t, $J=4.6\text{Hz}$), 7.05 (1H, d, $J=8.4\text{Hz}$), 7.22-7.31 (3H, m), 7.43-7.52 (5H, m), 7.57 (2H, d, $J=8.4\text{Hz}$), 7.78 (1H, s).

IR(KBr) ν : 3287, 2948, 1649 cm^{-1} .

Anal. for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_3 \cdot 0.2\text{H}_2\text{O}$:

Calcd: C, 75.69; H, 7.10; N, 6.09.

Found: C, 75.58; H, 6.93; N, 6.08.

10 Working Example 235 (Production of Compound 235)

In dichloromethane (10 ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.3 g), and to the suspension were added oxalyl chloride (0.27 ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 ml), and the mixture was dropwise added to a solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.25 g) and triethylamine (0.42 ml) in tetrahydrofuran (15 ml) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-(4-methylphenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methyl)aminomethyl)phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (0.45 g) as colorless crystals. mp 177-178°C.

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.63-1.77 (4H, m), 2.21 (3H, s), 2.40 (3H, s), 2.57-2.70 (1H, m), 3.08 (2H, t, $J=5.8\text{Hz}$), 3.26-3.44 (4H, m), 3.57 (2H, s), 4.01-4.11 (2H, m), 7.24-7.34 (3H, m), 7.40-7.57 (8H, m), 7.70 (1H, s).

IR(KBr) ν : 2949, 1651 cm^{-1} .

Anal. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2\text{S} \cdot 0.3\text{H}_2\text{O}$:

Calcd: C, 73.86; H, 6.92; N, 5.56.

Found: C, 73.93; H, 6.73; N, 5.82.

5 Working Example 236 (Production of Compound 236)

In dichloromethane (6 ml) was suspended 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.25 g), and to the suspension were added oxalyl chloride (0.24 ml) and dimethylformamide (catalytic amount) under ice-cooling. The mixture was stirred at room temperature for 1.5 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15 ml, and the mixture was dropwise added to a solution of 4-((N-methyl-N-(pentan-3-yl))aminomethyl)aniline (0.2 g) and triethylamine (0.38 ml) in tetrahydrofuran (15 ml) under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature for 5 hours, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-methyl-N-(pentan-3-yl))aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.23 g) as colorless crystals. mp 112-113°C.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.94 (6H, t, $J=7.3\text{Hz}$), 1.26-1.54 (4H, m), 2.14 (3H, s), 2.14-2.32 (3H, m), 2.40 (3H, s), 2.72 (2H, t, $J=6.4\text{Hz}$), 2.86-2.91 (2H, m), 3.55 (2H, s), 7.21-7.27 (3H, m), 7.31-7.56 (8H, m), 7.62 (1H, s).

IR(KBr) ν : 2930, 1651 cm^{-1} .

Anal. for $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}$:

Calcd: C, 82.36; H, 8.21; N, 6.00.

35 Found: C, 82.30; H, 8.05; N, 5.90.

Reference Example 180

To a mixture of 3-(4-methylphenyl)-6,7,8,9-tetrahydro-5H-benzocycloheptan-5-one (0.5 g), potassium carbonate (1.65 g) and 18-crown-6 (1.05 g) was added dimethylsulfoxide (10 ml). Under carbon dioxide atmosphere, the mixture was stirred at room temperature for 20 hours, poured into water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and subjected to back extraction with sodium hydroxide and water. The aqueous layer was collected, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated to precipitate colorless crystals (0.42 g), which were filtered with hexane and dissolved in ethanol (40 ml). To the mixture was added sodium boron hydride (0.54 g), and the mixture was stirred at room temperature for 1 hour. To the mixture was added water, and the mixture was concentrated, was acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated to give colorless crystals (0.41 g), which were dissolved in 80% formic acid (40 ml). The mixture was stirred at 100°C for 2.5 hours and concentrated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.14 g) as colorless crystals.

¹H-NMR(CDCl₃) δ: 2.04-2.18 (2H, m), 2.40 (3H, s), 2.70 (2H, t, J=6.8Hz), 2.86-2.91 (2H, m), 7.21-7.28 (3H, m), 7.44-7.56 (4H, m), 7.91 (1H, s).

Reference Example 181

In dimethylsulfoxide (15 ml) were dissolved 3-(4-methylphenyl)-6,7,8,9-tetrahydro-5H-benzocycloheptan-5-one (0.5 g) and 18-crown-6 (1.05 g). Under ice-cooling, potassium t-butoxide (1.65 g) was added to the solution. Under carbon dioxide atmosphere, the mixture was stirred at room temperature for 3 hours, poured into water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and subjected to back extraction with sodium hydroxide and water. The aqueous layer was collected, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated to precipitate colorless crystals (0.47 g), which were filtered with hexane and dissolved in ethanol (40 ml). To the mixture was added sodium boron hydride (0.58 g), and the mixture was stirred at room temperature for 1 hour. To the mixture was added water, and the mixture was concentrated, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated to precipitate colorless crystals (0.46 g), which were filtered with hexane. To the crystals was added 80% formic acid (10ml), and the mixture was refluxed for 1.5 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and subjected to back extraction with sodium hydroxide and water. The aqueous layer was collected, acidified with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was evaporated to precipitate 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.22 g) as colorless

crystals.

¹H-NMR(CDCl₃) δ: 2.04-2.16 (2H, m), 2.40 (3H, s), 2.69 (2H, t, J=6.7Hz), 2.86-2.91 (2H, m), 7.21-7.278 (3H, m), 7.44-7.56 (4H, m), 7.89 (1H, s).

5 Working Example 237 (Production of Compound 237)

In dimethylformamide (100 ml) was dissolved 7-(4-methylphenyl)-N-(4-((N-(4-oxocyclohexyl)-N-methyl)-aminomethyl)-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (7.5 g), and to the mixture was added methyl iodide (4.7 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added acetone to give dimethyl-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)-N-(4-oxocyclo-

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hexyl)ammonium iodide (8.9 g) as colorless crystals.
¹H-NMR(DMSO-d₆) δ: 2.09-2.24 (2H, m), 2.34 (3H, s), 2.41-2.61 (6H, m), 2.97 (6H, s), 2.97-3.00 (2H, m), 3.79-3.90 (1H, m), 4.31 (2H, t, J=4.4Hz), 4.56 (2H, s), 7.07 (1H, d, J=8.4Hz), 7.27 (2H, d, J=8.2Hz), 7.37 (1H, s), 7.55-7.60 (5H, m), 7.75 (1H, d, J=2.2Hz), 7.88 (2H, d, J=8.8Hz), 10.20 (1H, s).

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Working Example 238 (Production of Compound 238)

In dimethylformamide (5 ml) was dissolved in 2-(4-(1-pyrrolidinyl)phenyl)-N-(4-((N-tetrahydropyran-4-yl)-N-methyl)aminomethyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.15 g), and to the mixture was added methyl iodide (0.02 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. To the mixture was added ethyl acetate, and crude crystal was filtered. The crude crystal was recrystallized from ethanol-ethyl acetate to give dimethyl-(N-(2-(4-(1-pyrrolidinyl)phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carbonyl)-4-aminobenzyl)-4-tetrahydropyranylammonium iodide (0.05 g) as pale brown powder.

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¹H-NMR(DMSO-d₆) δ: 1.80-2.20 (10H, m), 2.63 (2H, t, J=5.6Hz), 2.81-2.84 (2H, m), 2.88 (6H, s), 3.24-3.44 (6H, m), 3.54-3.65

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(1H, m), 4.02-4.11 (2H, m), 4.46 (2H, s), 6.62 (2H, d, J=9.0Hz), 7.25 (1H, d, J=7.8Hz), 7.36-7.60 (7H, m), 7.88 (2H, d, J=8.4Hz), 10.22 (1H, s).

IR(KBr) ν : 2967, 1663, 1609 cm^{-1} .

5 Anal. for $\text{C}_{36}\text{H}_{44}\text{IN}_2\text{O}_2 \cdot \text{H}_2\text{O}$:

Calcd: C, 62.15; H, 6.66; N, 6.04.

Found: C, 61.89; H, 6.30; N, 5.97.

Working Example 239 (Production of Compound 239)

In dimethylformamide (5 ml) was dissolved N-(4-((N-3-hydroxypropyl-N-methyl)aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.2 g), and to the mixture was added methyl iodide (0.04 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate to give crude crystals, which were filtered and recrystallized from ethanol-ethyl acetate to give N-(3-hydroxypropyl)-N,N-dimethyl-(N-(2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carbonyl)-4-aminobenzyl)ammonium iodide (0.05 g) as colorless crystals.
mp 210-213°C.

$^1\text{H-NMR}(\text{CDCl}_3+\text{CD}_3\text{OD}) \delta$: 2.00-2.20 (4H, m), 2.40 (3H, s), 2.71 (2H, t, J=6.6Hz), 2.87-2.92 (2H, m), 3.10 (6H, s), 3.54-3.65 (2H, m), 3.73 (2H, t, J=5.3Hz), 4.63 (2H, s), 7.22-7.27 (3H, m), 7.43-7.58 (7H, m), 7.80 (2H, d, J=8.4Hz), 9.21 (1H, s).
IR(KBr) ν : 3337, 2934, 1653 cm^{-1} .

Anal. for $\text{C}_{31}\text{H}_{37}\text{IN}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O}$:

Calcd: C, 61.49; H, 6.33; N, 4.63.

Found: C, 61.55; H, 6.22; N, 4.74.

30 Working Example 240 (Production of Compound 240)

In dimethylformamide (5 ml) was dissolved N-(4-((N-3-hydroxypropyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.14 g), and to the mixture was added methyl iodide (0.04 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to

the residue was added ethyl acetate to give crude crystals, which were filtered and recrystallized from ethanol-ethyl acetate to give dimethyl-3-hydroxypropyl-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)ammonium iodide (0.15 g) as colorless crystals. mp 216-219°C.

¹H-NMR(CDCl₃+CD₃OD) δ: 2.00-2.20 (2H, m), 2.40 (3H, s), 3.06-3.10 (2H, m), 3.10 (6H, s), 3.51-3.61 (2H, m), 3.73 (2H, t, J=5.4Hz), 4.37 (2H, t, J=4.6Hz), 4.61 (2H, s), 7.07 (1H, d, J=8.4Hz), 7.25 (2H, d, J=8.2Hz), 7.46-7.59 (7H, m), 7.81 (2H, d, J=8.2Hz), 9.54 (1H, s).

IR(KBr) ν: 3306, 1651cm⁻¹.

Anal. for C₃₀H₃₅IN₂O₃·0.5H₂O:

Calcd: C, 59.31; H, 5.97; N, 4.61.

Found: C, 59.36; H, 5.95; N, 4.75.

Working Example 241 (Production of Compound 241)

In dimethylformamide (5 ml) was dissolved 7-(4-methylphenyl)-N-(4-((N-tetrahydropyran-4-yl-N-methyl)-aminomethyl)-phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (0.19 g), and to the mixture was added methyl iodide (0.03 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate to give crude crystals, which were filtered and recrystallized from ethanol-hexane to give dimethyl-(N-(7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carbonyl)-4-aminobenzyl)-N-(4-tetrahydropyranyl)ammonium iodide (0.2 g) as colorless crystals. mp 220-222°C(dec.).

¹H-NMR(DMSO-d₆) δ: 1.78-1.95 (2H, m), 2.05-2.20 (2H, m), 2.35 (3H, s), 2.88 (6H, s), 2.95-3.05 (2H, m), 3.21-3.32 (4H, m), 3.50-3.65 (1H, m), 4.05-4.15 (2H, m), 4.46 (2H, s), 7.29 (2H, d, J=8.0Hz), 7.46-7.63 (7H, m), 7.81-7.90 (3H, m), 10.34 (1H, s).

IR(KBr) ν: 2924, 1657cm⁻¹.

Working Example 242 (Production of Compound 242)

In dimethylformamide (5 ml) was dissolved N-(4-((N-methyl-N-(pentan-3-yl))aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.17 g), and to the mixture was added methyl iodide (0.08 ml). Under nitrogen atmosphere, the mixture was stirred at 45°C overnight. The solvent was evaporated, and to the residue was added ethyl acetate to give crude crystals, which were filtered and recrystallized from ethanol-ethyl acetate to give dimethyl-(N-(2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carbonyl)-4-aminobenzyl)-N-(pentan-3-yl)ammonium iodide (0.15 g) as colorless crystals.

mp 190-194°C(dec.).

¹H-NMR(CDCl₃) δ: 1.15 (6H, t, J=7.4Hz), 1.67-1.82 (2H, m), 2.05-2.25 (4H, m), 2.39 (3H, s), 2.73 (2H, t, J=6.6Hz), 2.80-2.90 (2H, m), 3.11 (6H, s), 3.40-3.51 (1H, m), 4.91 (2H, s), 7.18-7.26 (3H, m), 7.44 (1H, dd, J=1.8, 8.4Hz), 7.49 (2H, d, J=8.4Hz), 7.57-7.62 (4H, m), 7.80 (2H, d, J=8.4Hz), 8.35 (1H, s).

IR(KBr) ν: 2936, 1659cm⁻¹.

Anal. for C₃₃H₄₁IN₂O·0.5H₂O:

Calcd: C, 64.18; H, 6.85; N, 4.54.

Found: C, 63.84; H, 6.73; N, 4.47.

Reference Example 182

In DMF (50 ml) was dissolved N-cyclohexyl-N-methylamine (12.5 g, 0.11 mol), and to the solution were added potassium carbonate (27.6 g, 0.20 mol) and 4-nitrobenzylbromide (21.6 g, 0.10 mol). The mixture was stirred at room temperature for 5 hours. Under reduced pressure, the reaction mixture was concentrated. To the residue was added ethyl acetate, and the mixture was extracted with water. The ethyl acetate layer was washed with saturated sodium chloride solution, dried with MgSO₄, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give N-cyclohexyl-N-methyl-N-(4-

nitrobenzyl)amine (24.8 g).

¹H-NMR (200 MHz, CDCl₃) δ : 1.0-1.95 (10H, m), 2.19 (3H, s), 3.66 (2H, s), 7.51 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz).

Reference Example 183

- 5 To a solution of N-cyclohexyl-N-methyl-N-(4-nitrobenzyl)amine (12.4 g, 50.0 mmol) in methanol (250 ml) were added nickel bromide (1.09 g, 5.0 mmol) and then sodium boron hydride (7.57 g, 200 mmol) at 0°C, and the mixture was stirred at room temperature for 30 minutes. To the mixture
10 were added nickel bromide (0.55 g, 2.5 mmol) and then sodium boron hydride (3.78 g, 100 mmol) at 0°C, and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added water (100 ml), and the mixture was concentrated under reduced pressure. To the residue was
15 added ethyl acetate, and insoluble material was filtered off with Celite. The filtrate was washed with ethyl acetate, and the ethyl acetate layer was dried with MgSO₄ and concentrated under reduced pressure. The residue was washed with hexane to give 4-(N-cyclohexyl-N-methylamino-
20 methyl)aniline (3.99 g, 37%).

¹H-NMR (200 MHz, CDCl₃) δ : 1.0-1.95 (10H, m), 2.17 (3H, s), 2.3-2.55 (1H, m), 3.46 (2H, s), 3.59 (2H, br s), 6.65 (2H, d, J=8.5Hz), 7.10 (2H, d, J=8.5Hz).

Working Example 243 (Production of Compound 243)

- 25 To a solution of 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.28 g), 4-(N-cyclohexyl-N-methylaminomethyl)aniline (0.24 g) and 1-hydroxybenzotriazole (0.15 g) in dimethylformamide (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
30 hydrochloride (0.29 g) under ice-cooling. Under nitrogen atmosphere, the mixture was cooled to room temperature, and to the mixture were added 4-dimethylaminopyridine (3 mg) and triethylamine (0.42 ml). The mixture was stirred for 20 hours, poured into water, and extracted with ethyl acetate.
35 The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was washed with ethyl acetate and dried to give N-(4-(N-cyclohexyl-N-methylaminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide

5 (0.40 g).

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.0-1.95 (10H, m), 2.20 (3H, s), 2.35-2.55 (1H, m), 2.40 (3H, s), 3.0-3.15 (2H, m), 3.56 (2H, s), 4.3-4.45 (2H, m), 7.06 (1H, d, $J=8.4\text{Hz}$), 7.2-7.6 (11H, m).

Working Example 244 (Production of Compound 244)

10 In dimethylformamide (7 ml) was dissolved N-(4-(N-cyclohexyl-N-methylaminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.15 g), and to the mixture was added methyl iodide (0.06 ml). Under nitrogen atmosphere, the mixture was stirred at room
15 temperature for 20 hours. The solvent was evaporated, and to the residue was added ethyl acetate to give crude crystals, which were filtered and recrystallized from ethanol to give N-cyclohexyl-N,N-dimethyl-N-((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl)ammonium
20 iodide (0.15 g).

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.0-1.8 (6H, m), 1.9-2.05 (2H, m), 2.25-2.45 (2H, m), 2.36 (3H, s), 2.95-3.15 (8H, m), 3.45-3.7 (1H, m), 4.2-4.35 (2H, m), 4.83 (2H, s), 6.99 (1H, d, $J=8.4\text{Hz}$), 7.21 (2H, d, $J=7.6\text{Hz}$), 7.35-7.6 (6H, m), 7.74 (1H, d, $J=2.2\text{Hz}$), 7.85 (2H, d, $J=8.6\text{Hz}$), 8.79 (1H, s).

25 $\text{IR}(\text{KBr}) \nu$: 1659, 1609, 1593, 1518, 1493 cm^{-1} .

Working Example 245 (Production of Compound 245)

In dimethylformamide (5 ml) was dissolved N-(4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl)-7-(4-morpholino-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.20 g), and to the mixture was added methyl
30 iodide (0.03 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature for 32 hours. The solvent was evaporated, and the residue was purified with silica gel column chromatography (dichloromethane/methanol). The
35 desired fraction was concentrated, and to the residue was

added ethyl acetate. Insoluble material was filtered and recrystallized from ethanol to give dimethyl-N-(7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-aminobenzyl-N-(4-tetrahydropyranyl)ammonium iodide

5 (0.18 g).

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.6-2.0 (2H, m), 2.1-2.3 (2H, m), 2.92 (6H, s), 2.95-3.2 (6H, m), 3.35-3.55 (2H, m), 3.8-3.9 (4H, m), 4.0-4.35 (5H, m), 4.84 (2H, s), 6.85-7.05 (3H, m), 7.35-7.85 (9H, m), 8.92 (1H, s).

10 $\text{IR}(\text{KBr}) \nu$: 1659, 1609, 1520, 1495 cm^{-1} .

Reference Example 184

In tetrahydrofuran(100 ml) was dissolved 1,2-methylenedioxy-4-bromobenzene (24.0 g), and to the mixture was dropwise added n-butyllithium (1.6M hexane solution, 82 ml) at -55°C or less. The mixture was stirred at -70°C or less for 30 minutes. The resulting solution was dropwise added to a solution of trimethyl borate (18.6 g) in tetrahydrofuran (50 ml) at -60°C or less through cannula, and the mixture was stirred at -70°C or less for 1 hour and then for 2 hours while warming the mixture to room temperature. To the reaction mixture were added 1N hydrochloric acid (130 ml) and diethylether (150 ml), and the organic layer was separated. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated. The residue was washed with diisopropylether to give 3,4-methylene-dioxyphenyl borate (6.79 g).

25 $^1\text{H-NMR}(\text{DMSO}-d_6) \delta$: 5.99 (2H, s), 6.8-6.95 (1H, m), 7.25-7.45 (2H, m).

Reference Example 185

To a mixture of methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (0.57 g), 3,4-methylenedioxyphenyl borate(0.47 g) and sodium carbonate (0.42 g) were added water (2 ml) and 1,2-dimethoxyethane(12 ml). Under argon atmosphere, the mixture was stirred at room

temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (0.16 g). The mixture was stirred at 80°C for 14 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (0.43 g).

$^1\text{H-NMR}(\text{CDCl}_3) \delta$: 2.95-3.10 (2H, m), 3.83 (3H, s), 4.25-4.35 (2H, m), 6.01 (2H, s), 6.87 (1H, d, $J=8.6\text{Hz}$), 6.95-7.10 (3H, m), 7.40 (1H, dd, $J=8.4, 2.4\text{Hz}$), 7.47 (1H, d, $J=2.2\text{Hz}$), 7.65 (1H, s).

Reference Example 186

To methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (0.40 g) were added methanol (5 ml) and 1N sodium hydroxide (3.7 ml), and the mixture was stirred at room temperature for 20 hours. To the mixture was added 1N hydrochloric acid (3.7 ml), and the mixture was concentrated under reduced pressure. Precipitate was washed with water and diethylether and dried under reduced pressure to give 7-(3,4-methylene-dioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.32 g).

$^1\text{H-NMR}(\text{DMSO}-d_6) \delta$: 2.80-2.95 (2H, m), 4.15-4.35 (2H, m), 6.05 (2H, s), 6.97 (1H, d, $J=8.1\text{Hz}$), 7.01 (1H, d, $J=8.4\text{Hz}$), 7.16 (1H, dd, $J=8.1, 1.7\text{Hz}$), 7.29 (1H, d, $J=1.7\text{Hz}$), 7.53 (2H, dd, $J=8.4, 2.3\text{Hz}$), 7.63 (1H, s), 7.74 (1H, d, $J=2.3\text{Hz}$).

Working Example 246 (Production of Compound 246)

To a solution of 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.14 g), 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.11 g) and 1-hydroxy-benzotriazole (0.15 g) in dimethyl-formamide (10 ml) was added 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (0.13 g) under ice-cooling. Under nitrogen atmosphere, the reaction

mixture was warmed to room temperature. To the mixture were added 4-dimethylaminopyridine (3 mg) and triethylamine (0.19 ml), and the mixture was stirred for 18 hours, poured into water, and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give 7-(3,4-methylenedioxyphenyl)-4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.19 g).

¹H-NMR(CDCl₃) δ: 1.55-1.85 (4H, m), 2.21 (3H, s), 2.55-2.80 (1H, m), 3.00-3.15 (2H, m), 3.30-3.45 (2H, m), 3.58 (2H, s), 3.95-4.15 (2H, m), 4.30-4.45 (2H, m), 6.01 (2H, s), 6.88 (1H, d, J=8.6Hz), 6.95-7.10 (3H, m), 7.20-7.65 (7H, m). IR(KBr) ν: 1653, 1597, 1514, 1483cm⁻¹.

Working Example 247 (Production of Compound 247)

In dimethylformamide (5 ml) was dissolved 7-(3,4-methylenedioxyphenyl)-4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (95 mg), and to the mixture was added methyl iodide (0.012 ml). Under nitrogen atmosphere, the mixture was stirred at room temperature for 18 hours. The solvent was evaporated, and to the residue was added ethyl acetate. Insoluble material was filtered and recrystallized from ethanol to give dimethyl-N-(7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepin-4-carbonyl)-4-amino-benzyl-N-(4-tetrahydropyranyl)ammonium iodide (101 mg).

¹H-NMR(CDCl₃) δ: 1.7-2.0 (2H, m), 2.15-2.3 (2H, m), 2.85-3.1 (8H, m), 3.4-3.55 (2H, m), 4.0-4.35 (5H, m), 4.85 (2H, s), 5.96 (2H, s), 6.81 (1H, d, J=7.8Hz), 6.9-7.1 (3H, m), 7.25-7.7 (5H, m), 7.83 (2H, d, J=8.2 Hz), 8.89 (1H, s). IR(KBr) ν: 1659, 1609, 1520, 1495cm⁻¹.

Working Example 248 (Production of Compound 248)

In aqueous methanol was dissolved N,N-dimethyl-N-(4-(((2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclo-

hepten-8-yl)carbonyl)amino)benzyl)-N-(4-tetrahydro-
pyranyl)ammonium iodide (19 g), and the mixture was
subjected to ion exchange resin (DOWEX1-x8, 100-200 mesh,
Cl⁻ type) column, which was eluted with aqueous methanol.
5 The solvent of the desired fractions was evaporated, and
to the residue was added acetone to give crude crystals,
which were recrystallized from ethanol to give N,N-
dimethyl-N-(4-(((2-(4-methylphenyl)-6,7-dihydro-5H-
benzocyclohepten-8-yl)carbonyl)amino)benzyl)-N-(4-
10 tetrahydropyranyl)ammonium chloride (10.1 g) as
colorless crystals.

mp 226-232°C(dec.).

¹H-NMR(CDCl₃+CD₃OD) δ: 1.80-2.00 (2H, m), 2.07-2.26 (4H, m),
2.39 (3H, s), 2.72 (2H, t, J=6.6Hz), 2.85-2.91 (2H, m), 3.00
15 (6H, s), 3.54 (2H, t, J=11.3Hz), 4.00-4.21 (3H, m), 4.70
(2H, s), 7.21-7.29 (3H, m), 7.42-7.56 (7H, m), 7.81 (2H,
d, J=8.4Hz), 9.06 (1H, s).

IR(KBr) ν: 2934, 1655cm⁻¹.

Anal. for C₃₃H₃₉ClN₂O₂:

20 Calcd: C, 74.62; H, 7.40; N, 5.27; Cl, 6.67.

Found: C, 74.35; H, 7.33; N, 5.20; Cl, 6.80.

Working Example 248a (Production of Compound 248)

To a solution of N-(4-chloromethylphenyl)-2-(4-
methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-
25 carboxamide (9.38 g, 23.3 mmol) in DMF (50 ml) was dropwise
added a solution of N,N-dimethyl-N-tetrahydropyran-4-
ylamine (4.5 g, 35.0 mmol) in DMF (50 ml). Under nitrogen
atmosphere, the mixture was stirred for 23 hours. The
solvent was evaporated to give powder, which was washed with
30 acetone and dried. The resulting colorless powder was
recrystallized from ethanol to give N,N-dimethyl-N-(4-
(((2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-
8-yl)carbonyl)amino)benzyl)-N-(4-tetrahydropyranyl)-
ammonium chloride (Compound 248) (10.6 g, 86%) as colorless
35 powder.

Working Example 249 (Production of Compound 249)

In aqueous acetonitrile was dissolved N,N-dimethyl-N-(4-(((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)amino)benzyl)-N-(4-oxocyclohexyl)ammonium iodide (22.8 g), and the mixture was subjected to ion
5 exchange resin (DOWEX-SBR, Cl⁻ type) column, which was eluted with aqueous acetonitrile. The solvent of the desired fractions was evaporated, and the residue was dissolved in water. The mixture was subjected to freeze-drying to give
10 N,N-dimethyl-N-(4-(((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)amino)benzyl)-N-(4-oxocyclohexyl)ammonium chloride (Compound 249) (16.1 g) as colorless powder.

¹H-NMR(DMSO-d₆) δ: 2.05-2.25 (2H, m), 2.34 (3H, s), 2.41-2.61 (6H, m), 2.97 (6H, s), 2.97-3.00 (2H, m), 3.75-3.90
15 (1H, m), 4.30 (2H, t, J=4.4Hz), 4.57 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=7.8Hz), 7.45 (1H, s), 7.53-7.60 (5H, m), 7.78 (1H, d, J=2.2Hz), 7.92 (2H, d, J=8.4Hz), 10.34 (1H, s).

IR(KBr) ν: 3025, 2967, 1717, 1655cm⁻¹.

20 Anal. for C₃₃H₃₇ClN₂O₃·0.5H₂O:

Calcd: C, 71.53; H, 6.91; N, 5.06; Cl, 6.40.

Found: C, 71.21; H, 6.94; N, 4.94; Cl, 6.24.

Working Example 249a (Production of Compound 249)

To a solution of N-(4-chloromethylphenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
25 (214 mg, 0.530 mmol) in N,N-dimethylformamide (1 ml) was dropwise added a solution of 4-dimethylaminocyclohexanone (112 mg, 0.795 mmol) in N,N-dimethylformamide (1 ml). Under nitrogen atmosphere, the mixture was stirred for 14 hours.

30 The solvent was evaporated to give crude product, which was washed with ether to give N,N-dimethyl-N-(4-(((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)amino)benzyl)-N-(4-oxocyclohexyl)ammonium chloride (Compound 249) (305 mg) as colorless powder.

35 Working Example 250 (Production of Compound 250)

To a solution of N-(4-chloromethylphenyl)-7-(4-

ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide
(2.38 g) in DMF (20 ml) was added N,N-dimethyl-N-
tetrahydropyran-4-ylamine (1.42 g) at room temperature, and
the mixture was stirred for 14 hours. To the reaction mixture
5 was added ethyl acetate (100 ml) to precipitate crystals,
which were collected by filtration. The crystal was washed
with ethyl acetate to give crude product as pale yellow
crystals, which were recrystallized from ethanol to give
as N-(4-(((7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepin-
10 4-yl)carbonyl)amino)benzyl)-N,N-dimethyl-N-(4-
tetrahydropyranyl)ammonium chloride (Compound 250) (1.29
g) colorless crystals.

m.p. 200-204 °C

¹H-NMR (200MHz, DMSO-d₆) δ: 1.35 (3H, t, J=7.0 Hz), 1.75-
15 1.98 (2H, m), 2.06-2.24 (2H, m), 2.88 (6H, s), 2.94-3.05
(2H, m), 3.28-3.43 (2H, m), 3.49-3.69 (1H, m), 3.99-4.13
(2H, m), 4.07 (2H, q, J=7.0 Hz), 4.23-4.35 (2H, m), 4.47
(2H, s), 6.98-7.07 (3H, m), 7.37 (1H, s), 7.50-7.61 (5H,
m), 7.72 (1H, d, J=2.2 Hz), 7.87 (2H, d, J=8.4 Hz), 10.22
20 (1H, s).

IR (KBr) ν: 3425, 1647, 1603, 1520, 1489, 1407, 1317, 1294,
1240, 831 cm⁻¹

Anal. for C₃₃H₃₉N₂O₄Cl

Calcd: C, 70.38 ; H, 6.98 ; N, 4.97 ; Cl, 6.30

25 Found: C, 70.49 ; H, 7.08 ; N, 4.94 ; Cl, 6.19.

Working Example 250a (Production of Compound 250)

In aqueous methanol was dissolved N-(4-(((7-(4-
ethoxyphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)-
amino)benzyl)-N,N-dimethyl-N-(4-tetrahydropyranyl)-
30 ammonium iodide (26.6 g), and the mixture was subjected to
ion exchange resin (DOWEX-SBR, Cl⁻ type) column, which was
eluted with aqueous methanol. The solvent of the desired
fractions was evaporated, and to the residue was added
acetone to give crude crystals, which were recrystallized
35 from ethanol to give N-(4-(((7-(4-ethoxyphenyl)-2,3-
dihydro-1-benzoxepin-4-yl)carbonyl)amino)benzyl)-N,N-

dimethyl-N-(4-tetrahydropyranyl)ammonium chloride
(Compound 250) (16.6 g) as colorless crystals.

Working Example 251 (Production of Compound 251)

5 To a solution of N-(4-((N-tetrahydrothiopyran-4-yl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.2g) in dichloromethane (10ml) was added mCPBA (0.1g) at -10 to -20°C, and the mixture was stirred for 30 minutes. To the
10 mixture was added sodium thiosulfate solution, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was
15 evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give N-(4-((N-(1-oxotetrahydrothiopyran-4-yl)-N-methyl)-aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 251) (E,Z mixture:
20 0.12g) as colorless powder.

¹H-NMR(δ ppm, CDCl₃) 1.80-1.97 (2H, m), 2.17 (1.4H, s), 2.28 (1.6H, s), 2.37-2.51 (3H, m), 2.39 (3H, s), 2.56-2.73 (2H, m), 3.08 (2H, t, J=4.7Hz), 3.15-3.28 (2H, m), 3.54 (0.9H, s), 3.63 (1.1H, s), 4.36 (2H, t, J=4.7Hz), 7.06 (1H, d, J=8.4Hz), 7.23-7.34 (4H, m), 7.44-7.57 (6H, m), 7.64 (1H, s).

IR(KBr) ν: 3279, 2946, 1651cm⁻¹.

Anal. Calcd. for C₃₁H₃₄N₂O₃S: C, 72.34; H, 6.66; N, 5.44.

Found C, 72.31; H, 6.66; N, 5.35.

30 Working Example 252 (Production of Compound 252)

To a suspension of 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.15g) in dichloromethane (5ml) were added under ice-cooling oxalyl chloride (0.15ml) and dimethylformamide (catalytic
35 amount), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue

- was dissolved in tetrahydrofuran (15ml). The mixture was added dropwise, under ice-cooling, to a mixture of 1-(4-aminobenzyl)phosphorinane-1-oxide (0.13g) and triethylamine (0.23ml) in tetrahydrofuran (15ml). Under
- 5 nitrogen atmosphere, the mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the
- 10 solvent was evaporated to give crude crystals, which were recrystallized from ethanol/hexane to give 2-(4-methylphenyl)-N-(4-((1-oxophosphorinane-1-yl)methyl)-phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 252) (0.16g) as colorless crystals.
- 15 mp 282-283°C(dec.).
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.40-1.60 (2H, m), 1.70-1.80 (6H, m), 1.80-2.20 (4H, m), 2.40 (3H, s), 2.72 (2H, t, $J=6.6\text{Hz}$), 2.86-2.95 (2H, m), 3.16 (2H, d, $J=13.6\text{Hz}$), 7.15-7.26 (4H, m), 7.42-7.52 (5H, m), 7.60 (2H, d, $J=8.0\text{Hz}$), 7.80 (1H, s).
- 20 IR(KBr) ν : 2932, 1659 cm^{-1} .
Anal. Calcd. for $\text{C}_{31}\text{H}_{34}\text{NO}_2\text{P}\cdot 0.2\text{H}_2\text{O}$:
C, 76.43; H, 7.12; N, 2.87.
Found C, 76.20; H, 7.31; N, 3.00.
- Working Example 253 (Production of Compound 253)
- 25 To a suspension of 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.3g) in dichloromethane (5ml) were added under ice-cooling oxalyl chloride (0.3ml) and dimethylformamide (catalytic amount), and the mixture was stirred at room temperature for 2 hours.
- 30 The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (10ml). The mixture was added dropwise, under ice-cooling, to a mixture of 4-(N-methyl-N-(tetrahydrothiopyran-4-yl)-aminomethyl)aniline (0.27g) and triethylamine (0.45ml) in tetrahydrofuran (10ml). Under
- 35 nitrogen atmosphere, the mixture was stirred at room temperature for 4 hours. The solvent was evaporated, and

to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-tetrahydrothiopyran-4-yl-N-methyl)aminomethyl)-phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 253) (0.45g) as colorless crystals.

mp 177-178°C.

¹H-NMR (δ ppm, CDCl₃) 1.65-1.85 (2H, m), 2.14-2.20 (2H, m), 2.22 (3H, s), 2.40 (3H, s), 2.47-2.53 (1H, m), 2.68-2.72 (6H, m), 2.86-2.92 (2H, m), 3.58 (2H, s), 7.21-7.27 (2H, m), 7.31 (2H, d, J=8.4Hz), 7.42-7.52 (5H, m), 7.56 (2H, d, J=8.4Hz), 7.63 (1H, s).

IR(KBr) ν: 2932, 1651cm⁻¹.

Anal. Calcd. for C₃₂H₃₆N₂OS·0.2H₂O:

C, 76.82; H, 7.33; N, 5.60.

Found C, 76.89; H, 7.35; N, 5.64.

Working Example 254 (Production of Compound 254a and 254b)

To a solution of N-(4-((N-tetrahydrothiopyran-4-yl-N-methyl)aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.3g) in dichloromethane (20ml) was added mCPBA (0.18g) at -10 to -20°C, and the mixture was stirred for 1.5 hours. To the mixture was added sodium thiosulfate solution, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give two kinds of crude crystals, each of which was recrystallized from ethyl acetate/ethanol/hexane to give (E) or (Z)-N-(4-((N-(1-oxotetrahydrothiopyran-4-yl)-N-

- 5 methyl)aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 254a) (76mg) and (Z) or (E)-N-(4-((N-(1-oxotetrahydrothiopyran-4-yl)-N-methyl)aminomethyl)phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 254b) (0.11g) as colorless crystals, respectively.

Compound 254a:

mp 218-219°C.

- 10 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.80-2.00 (2H, m), 2.10-2.20 (2H, m), 2.19 (3H, s), 2.25-2.39 (2H, m), 2.40 (3H, s), 2.61-2.76 (5H, m), 2.86-2.92 (2H, m), 3.23-3.33 (2H, m), 3.57 (2H, s), 7.22-7.31 (4H, m), 7.42-7.52 (5H, m), 7.58 (2H, d, $J=8.4\text{Hz}$), 7.66 (1H, s).

- 15 Anal. Calcd. for $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_2\text{S}\cdot 0.2\text{H}_2\text{O}$:

C, 74.44; H, 7.11; N, 5.43.

Found C, 74.43; H, 7.18; N, 5.66.

Compound 254b:

mp 216-218°C.

- 20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.80-2.00 (3H, m), 2.10-2.25 (3H, m), 2.35 (3H, s), 2.40 (3H, s), 2.44-2.53 (2H, m), 2.69-2.76 (3H, m), 2.86-2.92 (2H, m), 3.07-3.17 (2H, m), 3.71 (2H, s), 7.22-7.27 (2H, m), 7.35-7.52 (7H, m), 7.60 (2H, d, $J=8.4\text{Hz}$), 7.73 (1H, s).

- 25 Working Example 255 (Production of Compound 255)

- In dichloromethane (5ml) was suspended 2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.3g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.3ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the solution was added dropwise, under ice-cooling, to a solution of 4-(N-ethyl-N-(tetrahydropyran-4-yl)amino-30 methyl)aniline (0.27g) and triethylamine (0.45ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the
- 35

mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-ethyl-N-tetrahydropyran-4-yl)aminomethyl)-phenyl)-2-(4-methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 255) (0.38g) as colorless crystals.

mp 122-123°C.

¹H-NMR(δ ppm, CDCl₃) 1.01 (3H, t, J=7.1Hz), 1.62-1.72 (4H, m), 2.13-2.19 (2H, m), 2.40 (3H, s), 2.57 (2H, q, J=7.1Hz), 2.69-2.76 (3H, m), 2.86-2.92 (2H, m), 3.34 (2H, dt, J=3.4, 10.9Hz), 3.62 (2H, s), 3.97-4.04 (2H, m), 7.21-7.28 (3H, m), 7.35 (2H, d, J=8.6Hz), 7.42-7.57 (6H, m), 7.62 (1H, s). IR(KBr) ν: 2936, 1651cm⁻¹.

Anal. Calcd. for C₃₃H₃₈N₂O₂: C, 80.13; H, 7.74; N, 5.66.
Found C, 79.96; H, 7.77; N, 5.38.

Working Example 256 (Production of Compound 256)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.3g) in dichloromethane (6ml) were added, under ice-cooling, oxalyl chloride (0.25ml) and dimethylformamide (catalytic amount), and the mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (15ml). The mixture was added dropwise, under ice-cooling, to a solution of 4-((N-methyl-N-(pentan-3-yl)aminomethyl)-aniline (0.23g) and triethylamine (0.42ml) in tetrahydrofuran (15ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and

saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-
5 ((N-methyl-N-(pentan-3-yl)amino)methyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 256) (0.34g) as colorless crystals.
mp 136-137°C.

¹H-NMR(δ ppm, CDCl₃) 0.94 (6H, t, J=7.3Hz), 1.26-1.54 (4H,
10 m), 2.13 (3H, s), 2.17-2.32 (1H, m), 2.40 (3H, s), 3.08 (2H, t, J=5.9Hz), 3.29 (2H, t, J=5.9Hz), 3.55 (2H, s), 7.24-7.28 (2H, m), 7.31-7.40 (3H, m), 7.44-7.57 (6H, m), 7.66 (1H, s).

IR(KBr) ν: 2959, 2928, 1651cm⁻¹.

15 Anal. Calcd. for C₃₁H₃₆N₂OS: C, 76.82; H, 7.49; N, 5.78.
Found C, 76.77; H, 7.21; N, 5.63.

Working Example 257 (Production of Compound 257)

In dichloromethane (5ml) was suspended 7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid
20 (0.25g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.23ml) and dimethylformamide (catalytic amount).

The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved
25 in tetrahydrofuran (20ml), and the mixture was added dropwise, under ice-cooling, to a solution of 2-(N-(4-aminobenzyl)-N-methylamino)-1,3-propanediol (0.21g) and triethylamine (0.37ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room
30 temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was
35 evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give

crude crystals, which were recrystallized from ethyl acetate/ ethanol/hexane to give N-(4-((N-bis(hydroxymethyl)methyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide

- 5 (Compound 257) (0.22g) as colorless crystals.
mp 199-201°C.

¹H-NMR(δ ppm, CDCl₃) 2.30 (3H, s), 2.39 (3H, s), 2.96-3.03 (1H, m), 3.08 (2H, t, J=4.5Hz), 3.61-3.73 (4H, m), 3.78 (2H, s), 4.36 (2H, t, J=4.5Hz), 7.06 (1H, d, J=8.4Hz), 7.23-
10 7.32 (4H, m), 7.44-7.58 (6H, m), 7.62 (1H, s).
IR(KBr) ν: 3260, 2928, 1653cm⁻¹.

Anal. Calcd. for C₂₉H₃₂N₂O₄·0.2H₂O:

C, 73.15; H, 6.86; N, 5.88.

Found C, 73.20; H, 6.86; N, 5.91.

- 15 Working Example 258 (Production of Compound 258)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.3g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.28ml) and dimethylformamide (catalytic
20 amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and the mixture was added dropwise, under ice-cooling, to a solution of N-(4-aminobenzyl)sarcosine methyl ester (0.25g) and
25 triethylamine (0.45ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and
30 saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give crude crystals, which were recrystallized from ethyl acetate/hexane to give
35 N-(4-((N-methoxycarbonylmethyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-

carboxamide (Compound 258) (0.38g) as colorless crystals.
mp 135-136°C.

¹H-NMR(δ ppm, CDCl₃) 2.39 (3H, s), 2.39 (3H, s), 3.08 (2H, t, J=4.4Hz), 3.26 (2H, s), 3.65 (2H, s), 3.72 (3H, s), 4.36
5 (2H, t, J=4.4Hz), 7.06 (1H, d, J=8.4Hz), 7.22-7.36 (4H, m),
7.43-7.60 (7H, m).

IR(KBr) ν: 3262, 2951, 1740cm⁻¹.

Anal. Calcd. for C₂₉H₃₀N₂O₄: C, 74.02; H, 6.43; N, 5.95.
Found C, 74.07; H, 6.47; N, 5.94.

10 Working Example 259 (Production of Compound 259)

In methanol (20ml) and THF (10ml) was dissolved N-(4-((N-methoxycarbonylmethyl-N-methyl)aminomethyl)-phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (0.24g), and to the mixture was added 1N sodium
15 hydroxide solution (3.0ml). The mixture was stirred at room temperature overnight and concentrated. The residue was neutralized with 1N hydrochloric acid, and precipitated materials were filtered and dissolved in methanol. The mixture was filtered, and to the filtrate was added 4N
20 hydrochloric acid-ethyl acetate. The solvent was evaporated, and the residue was purified with methanol/diethylether to give N-(4-((N-carboxymethyl-N-methyl)-aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide hydrochloride (Compound 259)
25 (0.21g) as pale yellow amorphous.

¹H-NMR(δ ppm, DMSO-d₆) 2.34 (3H, s), 2.76 (3H, s), 2.99 (2H, br), 3.36 (2H, br), 4.02 (2H, s), 4.30 (2H, br), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=7.8Hz), 7.38 (1H, s), 7.48 (2H, d, J=8.6Hz), 7.55-7.59 (3H, m), 7.76 (1H, d, J=2.2Hz), 7.82
30 (2H, d, J=8.6Hz), 10.18 (1H, s).

IR(KBr) ν: 1744cm⁻¹.

Anal. Calcd. for C₂₈H₂₉ClN₂O₄·0.5H₂O:]

C, 66.99; H, 6.02; N, 5.58.

Found C, 66.93; H, 5.87; N, 5.11.

35 Working Example 260 (Production of Compound 260)

In dichloromethane (10ml) was suspended 7-(4-methyl-

phenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.3g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.25ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and the mixture was added dropwise, under ice-cooling, to a solution of N-(4-aminobenzyl)sarcosine methyl ester (0.23g) and triethylamine (0.42ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-methoxycarbonylmethyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 260) (0.43g) as colorless crystals. mp 148-150°C.

¹H-NMR(δ ppm, CDCl₃) 2.39 (3H, s), 2.40 (3H, s), 3.08 (2H, t, J=6.0Hz), 3.26 (2H, s), 3.29 (2H, t, J=6.0Hz), 3.66 (2H, s), 3.72 (3H, s), 7.24-7.58 (11H, m), 7.67 (1H, s).

IR(KBr) ν: 1738cm⁻¹.

Anal. Calcd. for C₂₉H₃₀N₂O₃S: C, 71.58; H, 6.21; N, 5.76.

Found C, 71.75; H, 5.95; N, 5.60.

Working Example 261 (Production of Compound 261)

In methanol (20ml) and THF (10ml) was dissolved N-(4-((N-methoxycarbonylmethyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (0.23g), and to the mixture was added 1N sodium hydroxide solution (2.4ml). The mixture was stirred at room temperature overnight, concentrated and neutralized with 1N hydrochloric acid. Precipitated materials were filtered, washed with water and recrystallized from

ethanol/hexane to give N-(4-((N-carboxymethyl-N-methyl)aminomethyl)phenyl)-7-(4-methyl-phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 261) (0.16g) as colorless crystals.

5 mp 243-245°C.

¹H-NMR(δ ppm, DMSO-d₆) 2.34 (6H, br), 3.00 (2H, br), 3.16 (2H, br), 3.22 (2H, br), 3.80 (2H, br), 7.20-7.35 (4H, m), 7.45-7.72 (7H, m), 7.82 (1H, s), 10.14 (1H, s).

Anal. Calcd. for C₂₈H₂₈N₂O₃S·0.5H₂O:

10 C, 69.83; H, 6.07; N, 5.82.

Found C, 69.62; H, 5.92; N, 5.58.

Working Example 262 (Production of Compound 262)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.2g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.18ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated.

The residue was dissolved in tetrahydrofuran (20ml), and 20 the mixture was added dropwise, under ice-cooling, to a solution of 1-(N-(4-aminobenzyl)-N-methylamino)-3-propanol (0.15g) and triethylamine (0.28ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The 25 solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with 30 silica gel column (methanol/ triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-3-hydroxypropyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 262) 35 (0.16g) as colorless crystals.
mp 147-148°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.69-1.80 (2H, m), 2.25 (3H, s), 2.40 (3H, s), 2.67 (2H, t, $J=5.6\text{Hz}$), 3.08 (2H, t, $J=5.9\text{Hz}$), 3.28 (2H, t, $J=5.9\text{Hz}$), 3.53 (2H, s), 3.78 (2H, t, $J=5.3\text{Hz}$), 7.24-7.32 (3H, m), 7.41-7.50 (4H, m), 7.53-7.60 (4H, m),

5 7.81 (1H, s).

IR(KBr) ν : 3266, 2948, 1649 cm^{-1} .

Anal. Calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_2\text{S}\cdot 0.3\text{H}_2\text{O}$:

C, 72.86; H, 6.87; N, 5.86.

Found C, 72.90; H, 6.70; N, 6.05.

10 Working Example 263 (Production of Compound 263)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.2g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.19ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated.

15 The residue was dissolved in tetrahydrofuran (20ml), and the mixture was added dropwise, under ice-cooling, to a solution of 4-((N-3-methoxypropyl-N-methyl)amino-methyl)aniline (0.16g) and triethylamine (0.3ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-3-methoxypropyl-N-methyl)aminomethyl)phenyl)-7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 263) (0.28g) as colorless crystals.
mp 121-123°C.

35 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.75-1.84 (2H, m), 2.19 (3H, s), 2.40 (3H, s), 2.45 (2H, t, $J=7.3\text{Hz}$), 3.09 (2H, t, $J=4.6\text{Hz}$), 3.33 (3H, s), 3.43 (2H, t, $J=6.6\text{Hz}$), 3.47 (2H, s), 4.37 (2H, t, $J=4.6\text{Hz}$), 7.06 (1H, d, $J=8.2\text{Hz}$), 7.23-7.33 (4H, m),

7.44-7.56 (7H, m).

IR(KBr) ν : 2934, 1653 cm^{-1} .

Anal. Calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3$: C, 76.57; H, 7.28; N, 5.95.

Found C, 76.41; H, 7.24; N, 6.02.

5 Working Example 264 (Production of Compound 264)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.15g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.15ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the mixture was added dropwise, under ice-cooling, to a solution of 4-((N-3-methoxypropyl-N-methyl)amino-methyl)aniline (0.12g) and triethylamine (0.21ml) in tetrahydrofuran (10ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-3-methoxypropyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 264) (0.18g) as colorless crystals. mp 128-129°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.70-1.87 (2H, m), 2.19 (3H, s), 2.40 (3H, s), 2.45 (2H, t, $J=8.4\text{Hz}$), 3.08 (2H, t, $J=5.6\text{Hz}$), 3.29 (2H, t, $J=5.6\text{Hz}$), 3.33 (3H, s), 3.43 (2H, t, $J=6.4\text{Hz}$), 3.47 (2H, s), 7.24-7.33 (3H, m), 7.40-7.58 (8H, m), 7.68 (1H, s).

IR(KBr) ν : 2924, 1651 cm^{-1} .

Anal. Calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_2\text{S}$: C, 74.04; H, 7.04; N, 5.76.

Found C, 73.80; H, 6.95; N, 5.87.

Working Example 265 (Production of Compound 265)

In dichloromethane (5ml) was suspended 2-(4-methyl-phenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (0.2g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.19ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the mixture was added dropwise, under ice-cooling, to a solution of (4-aminophenyl)-(2-pyridyl)methanol (0.15g) and triethylamine (0.3ml) in tetrahydrofuran (15ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 2-(4-methylphenyl)-N-(4-hydroxy(2-pyridyl)methylphenyl)-6,7-dihydro-5H-benzocyclo-heptene-8-carboxamide (Compound 265) (0.30g) as colorless crystals.
mp 195-196°C.

¹H-NMR (δ ppm, CDCl₃) 2.12-2.18 (2H, m), 2.39 (3H, s), 2.71 (2H, t, J=6.2Hz), 2.85-2.91 (2H, m), 5.31 (1H, d, J=3.8Hz), 5.75 (1H, d, J=3.8Hz), 7.12-7.26 (4H, m), 7.35-7.67 (11H, m), 8.57 (1H, d, J=5.4Hz).

IR(KBr) ν: 2930, 1651cm⁻¹.

Anal. Calcd. for C₃₁H₂₆N₂O₂·0.2H₂O:

C, 80.21; H, 6.17; N, 6.04.

Found C, 80.15; H, 6.05; N, 6.13.

Working Example 266 (Production of Compound 266)

In dichloromethane (25ml) was dissolved 2-(4-methyl-phenyl)-N-(4-hydroxy(2-pyridyl)methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (0.2g), and to the mixture was added, under ice-cooling, mCPBA (0.14g). The mixture was stirred at room temperature

overnight, and to the mixture was added sodium thiosulfate solution. The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and
5 dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give crude crystals, which were
10 recrystallized from ethyl acetate/hexane to give 2-(4-methylphenyl)-N-(4-hydroxy(1-oxidepyridin-2-yl)methylphenyl)-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 266) (0.12g) as colorless crystals.

mp 127-128°C.

¹H-NMR(δ ppm, CDCl₃) 2.14-2.20 (2H, m), 2.40 (3H, s), 2.73
15 (2H, t, J=6.4Hz), 2.87-2.92 (2H, m), 6.07 (1H, s), 6.40 (1H, br), 6.93-6.98 (1H, m), 7.22-7.28 (4H, m), 7.43-7.53 (7H, m), 7.67 (2H, d, J=8.8Hz), 7.75 (1H, s), 8.24-8.28 (1H, m).
IR(KBr) ν: 2928, 1651cm⁻¹.

Anal. Calcd. for C₃₁H₂₈N₂O₃·0.5H₂O:

20 C, 76.68; H, 6.02; N, 5.77.

Found C, 76.59; H, 6.00; N, 5.65.

Working Example 267 (Production of Compound 267)

In dimethylformamide (5ml) was dissolved N-(4-(piperidin-2-ylcarbonyl)phenyl)-7-(4-methylphenyl)-2,3-
25 dihydro-1-benzoxepine-4-carboxamide (0.2g), and to the mixture were added sodium hydrogen carbonate (0.05g) and methyl iodide (0.1ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl
30 acetate to give crude crystals, which were recrystallized from ethanol/ethyl acetate to give N,N-dimethyl-2-(4-((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carbonyl)amino)benzoyl)piperidinium iodide (Compound 267) (0.16g) as colorless powder.

35 mp 236-237°C(dec.).

¹H-NMR(δ ppm, CDCl₃) 1.75-2.10 (4H, m), 2.15-2.38 (2H, m),

2.38 (3H, s), 3.07 (2H, t, J=4.6Hz), 3.43 (3H, s), 3.53 (3H, s), 3.62-3.68 (1H, m), 4.34 (2H, t, J=4.6Hz), 4.68 (1H, br), 6.41-6.45 (1H, m), 7.03 (1H, d, J=8.4Hz), 7.22 (2H, d, J=8.0Hz), 7.43-7.52 (4H, m), 7.73 (1H, d, J=2.2Hz), 7.95 (2H, d, J=9.2Hz), 8.34 (2H, d, J=8.8Hz), 8.59 (1H, s).
IR(KBr) ν : 2955, 1674 cm^{-1} .

Anal. Calcd. for $\text{C}_{32}\text{H}_{35}\text{IN}_2\text{O}_3 \cdot 0.5\text{H}_2\text{O}$:

C, 60.86; H, 5.75; N, 4.44.

Found C, 60.89; H, 5.49; N, 4.52.

10 Working Example 268 (Production of Compound 268)

To a solution of 2-methyl-6-(4-methylphenyl)-quinoline-3-carboxylic acid (120mg) and 1-hydroxy-benzotriazole (88mg) in DMF (5ml) was added at room temperature 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (125mg), and the mixture was stirred for 1 hour. To the mixture was added a solution of 1-(4-aminobenzyl)phosphorinane-1-oxide (109mg) and triethylamine (0.1ml) in DMF (3ml), and the mixture was stirred for 3 days. Under reduced pressure, the mixture was concentrated, and to the residue was added water. The mixture was extracted with chloroform, and the organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was separated and purified with column chromatography (ethanol/ethyl acetate=1:2) and recrystallized from (ethanol/ethyl acetate) to give pale yellow crystals of 2-methyl-6-(4-methylphenyl)-N-(pentamethylenephosphorylmethylphenyl)quinoline-3-carboxamide (Compound 268) (116.1mg).

30 m.p. 273-275 $^{\circ}\text{C}$

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.01-1.84 (10H, m), 2.44 (3H, s), 2.90 (3H, s), 3.04 (2H, d, J=12.6 Hz), 7.17-7.25 (2H, m), 7.32 (2H, d, J=7.9 Hz), 7.61 (2H, d, J=7.9 Hz), 7.69 (2H, d, J=8.2 Hz), 7.99-8.13 (3H, m), 8.30 (1H, s), 9.44 (1H, br s).

IR (KBr) 3024, 1664, 1601, 1539, 1516, 1319, 1159, 847, 816

cm⁻¹Anal. Calcd. for C₃₀H₃₁N₂O₂P·0.3H₂O

Calcd. C, 73.84 ; H, 6.53 ; N, 5.74 ; P, 6.35.

Found. C, 73.67 ; H, 6.58 ; N, 5.67 ; P, 6.27.

5 Working Example 269 (Production of Compound 269)

Under nitrogen atmosphere, to a solution of (E)-3-[5-(4-isopropylphenyl)thiophen-2-yl]acrylic acid (130mg) in THF (10ml) was added at room temperature oxalyl chloride (0.07ml) and then a drop of DMF, and the mixture was stirred
10 for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added 1-(4-aminobenzyl)-phosphorinane-1-oxide (117mg) and triethylamine (0.15ml) at 0°C, and the mixture was stirred at room temperature for
15 4 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate, concentrated and purified with column chromatography (ethanol/ethyl acetate=1:4) and
20 recrystallized from ethanol/ethyl acetate to give yellow crystals of (E)-3-[5-(4-methylphenyl)thiophen-2-yl]-N-(pentaethylenephosphorylmethylphenyl)acrylamide (Compound 269) (60.5mg).

m.p. 295 °C(dec.)

25 ¹H-NMR (200MHz, CDCl₃) δ 1.28 (6H, d, J=7.0 Hz), 1.51-2.10 (10H, m), 2.89-3.00 (1H, m), 3.15 (2H, d, J=13.2 Hz), 6.48 (1H, d, J=15.0 Hz), 7.15-7.33 (6H, m), 7.50-7.62 (4H, m), 7.82 (1H, d, J=15.0 Hz), 8.37-8.59 (1H, m).

IR (KBr) 3057, 1672, 1618, 1543, 1510, 1412, 1356, 1327,
30 1250, 1232, 1165, 960, 852, 829, 793 cm⁻¹

Anal. Calcd. For C₂₈H₃₂NO₂SP

Calcd. C, 70.41 ; H, 6.75 ; N, 2.93.

Found. C, 70.06 ; H, 6.82 ; N, 2.98.

Working Example 270 (Production of Compound 270)

35 Under nitrogen atmosphere, to a solution of (E)-3-[5-(4-tert-butylphenyl)thiophen-2-yl]acrylic acid (120mg)

in THF (10ml) were added at room temperature oxalyl chloride (0.06ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture
5 were added at 0°C 1-(4-aminobenzyl)phosphorinane-1-oxide (104mg) and triethylamine (0.12ml), and the mixture was stirred at room temperature for 18 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed
10 with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give yellow crystals of (E)-N-(4-pentamethylene
15 phosphorylmethylphenyl)-3-[5-(4-tert-butylphenyl)-thiophen-2-yl]acrylamide (Compound 270) (82.1mg).
m.p. >300 °C

¹H-NMR (200MHz, CDCl₃) δ 1.35 (9H, s), 1.50-2.22 (10H, m),
3.15 (2H, d, J=13.2 Hz), 6.53 (1H, d, J=15.4 Hz), 7.12-
20 7.30 (4H, m), 7.42 (2H, d, J=8.4 Hz), 7.49-7.60 (4H, m),
7.82 (1H, d, J=15.4 Hz), 8.79-8.98 (1H, m).
IR (KBr) 3238, 1672, 1618, 1543, 1514, 1358, 1252, 1167,
852, 793 cm⁻¹

Anal. Calcd. For C₂₉H₃₄NO₂SP
25 Calcd. C, 70.85 ; H, 6.97 ; N, 2.85 ; P, 6.30.
Found. C, 70.61 ; H, 6.90 ; N, 2.89 ; P, 6.17.

Working Example 271 (Production of Compound 271)

Under nitrogen atmosphere, to a solution of 2-(4-methylphenyl)benzofuran-5-carboxylic acid (130mg) in THF
30 (10ml) were added at room temperature oxalyl chloride (0.07ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 1-(4-aminobenzyl)phosphorinane-1-oxide
35 (126mg) and triethyl-amine (0.15ml), and the mixture was stirred at room temperature for 3 hour. The mixture was

- added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated. The resulting crystals were recrystallized
- 5 from ethanol to give colorless crystals of 2-(4-methylphenyl)-N-(4-pentamethylenephosphorylmethyl-phenyl)benzofuran-5-carboxamide (Compound 271) (134.6mg). m.p. 297-296 °C
- ¹H-NMR (200MHz, CDCl₃) δ 1.42-2.16 (10H, m), 2.42 (3H, s),
- 10 3.17 (2H, d, J=13.2 Hz), 7.04 (1H, s), 7.24-7.33 (4H, m), 7.58 (1H, d, J=8.6 Hz), 7.67 (2H, d, J=8.4 Hz), 7.76-7.85 (3H, m), 8.14 (1H, d, J=1.8 Hz), 8.15-8.19 (1H, m). IR (KBr) 3390, 2929, 1657, 1524, 1323, 1230, 1161, 1132, 849, 824, 800, 760 cm⁻¹
- 15 Anal. Calcd. For C₂₈H₂₈NO₃P
Calcd. C, 73.51 ; H, 6.17 ; N, 3.06.
Found. C, 73.45 ; H, 5.89 ; N, 2.83.
- Working Example 272 (Production of Compound 272)
- To a solution of 2-(4-methylphenyl)benzofuran-6-
- 20 carboxylic acid (130mg) in THF (10ml) were added oxalyl chloride (0.07ml) and a drop of dimethylformamide at room temperature, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were
- 25 added at 0°C 1-(4-aminobenzyl)phosphorinane-1-oxide (126mg) and triethylamine (0.15ml), and the mixture was stirred at room temperature for 20 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with dichloromethane, and the organic layer was
- 30 washed with saturated brine. Under reduced pressure, the mixture was concentrated, and the residue was recrystallized from ethanol to give pale yellow crystals of 2-(4-methyl-phenyl)-N-(4-pentamethylenephosphoryl-methylphenyl)benzofuran-6-carboxamide (Compound 272)
- 35 (149.9mg).
m.p. >300 °C

IR (KBr) 3224, 1651, 1535, 1512, 1323, 1165, 845, 820 cm^{-1}

Anal. Calcd. For $\text{C}_{28}\text{H}_{28}\text{NO}_3\text{P}$

Calcd. C, 73.51 ; H, 6.17 ; N, 3.06.

Found. C, 73.50 ; H, 6.17 ; N, 2.92.

5 Working Example 273 (Production of Compound 273)

To a solution of 7-(4-methylsulfonylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (100mg) in THF (10ml) were added at room temperature oxalyl chloride (0.05ml) and a drop of DMF, and the mixture was stirred for 10 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)-aminomethyl]aniline (71mg) and triethylamine (0.1ml), and the mixture was stirred at room temperature for 16 hours. 15 The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column 20 chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give colorless crystals of 7-(4-methylsulfonylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 273) (123mg).

25 m.p. 233-235 °C

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.62-1.82 (4H, m), 2.21 (3H, s), 2.56-2.73 (1H, m), 3.04-3.15 (2H, m), 3.10 (3H, s), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.99-4.09 (2H, m), 4.39 (2H, t, $J=4.5$ Hz), 7.12 (1H, d, $J=8.4$ Hz), 7.24-7.35 (3H, m), 7.46-7.60 (5H, m), 7.74 (2H, d, $J=8.6$ Hz), 8.00 (2H, d, $J=8.6$ Hz). 30

IR (KBr) 3292, 1645, 1524, 1308, 1144 cm^{-1}

Anal. Calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_5\text{S}$

Calcd. C, 68.11 ; H, 6.27 ; N, 5.12 ; S, 5.87.

Found. C, 67.94 ; H, 6.40 ; N, 5.09 ; S, 5.90.

35 Working Example 274 (Production of Compound 274)

Under nitrogen atmosphere, to a solution of (E)-3-

[5-(4-isopropylphenyl)thiophen-2-yl]acrylic acid (130mg) in THF (10ml) were added at room temperature oxalyl chloride (0.07ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (116mg) and triethylamine (0.15ml), and the mixture was stirred at room temperature for 4 hour.

The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate, concentrated and purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate/hexane to give yellow crystals of (E)-3-[5-(4-isopropylphenyl)thiophen-2-yl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]acrylamide (Compound 274) (162.9mg).

m.p. 187-189 °C

¹H-NMR (200MHz, CDCl₃) δ 1.27 (6H, d, J=6.8 Hz), 1.54-1.84 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 2.84-3.01 (1H, m), 3.30-3.44 (2H, m), 3.56 (2H, s), 3.97-4.10 (2H, m), 6.31 (1H, d, J=15.4 Hz), 7.19-7.35 (7H, m), 7.49-7.61 (4H, m), 7.84 (1H, d, J=15.4 Hz).

IR (KBr) 3315, 1664, 1606, 1535, 1512, 1408, 1335, 1169, 829, 804 cm⁻¹

Anal. Calcd. for C₂₉H₃₄N₂O₂S

Calcd. C, 73.38 ; H, 7.22 ; N, 5.90 ; S, 6.76.

Found. C, 73.12 ; H, 7.34 ; N, 5.88 ; S, 6.83.

Working Example 275 (Production of Compound 275)

A solution of 7-(4-methylthiophenyl)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (110mg) and sodium periodate (48mg) in methanol/water (40/15ml) was stirred at room temperature for 2 days. Under reduced pressure, the mixture was concentrated, and to the residue was added water. The mixture was extracted with chloroform.

The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:1) and recrystallized from ethanol/ethyl acetate to give colorless crystals of 7-(4-methylsulfinylphenyl)-N-[4-[N-methyl-N-(4-tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 275) (15.5mg).

¹H-NMR (200MHz, CDCl₃) δ 1.52-1.83 (4H, m), 2.21 (3H, s), 2.52-2.74 (1H, m), 2.77 (3H, s), 3.10 (2H, t, J=4.4 Hz), 3.29-3.43 (2H, m), 3.57 (2H, s), 3.98-4.10 (2H, m), 4.39 (2H, t, J=4.4 Hz), 7.11 (1H, d, J=8.0 Hz), 7.23-7.35 (3H, m), 7.44-7.63 (5H, m), 7.71 (4H, s).

IR (KBr) 3327, 1649, 1515, 1410, 1315, 1240, 1038, 822 cm⁻¹
Working Example 276 (Production of Compound 276)

Under nitrogen atmosphere, to a solution of (E)-3-[5-(4-tert-butylphenyl)thiophen-2-yl]acrylic acid (130mg) in THF (10ml) were added at room temperature oxalyl chloride (0.06ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (109mg) and triethylamine (0.13ml), and the mixture was stirred at room temperature for 6 days. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated. The residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethyl acetate/hexane to give yellow crystals of (E)-3-[5-(4-tert-butylphenyl)thiophen-2-yl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]acrylamide (Compound 276) (107.3mg).
m.p. 216-220 °C

¹H-NMR (200MHz, CDCl₃) δ 1.35 (9H, s), 1.50-1.86 (4H, m),

2.21 (3H, s), 2.51-2.76 (1H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 3.99-4.10 (2H, m), 6.32 (1H, d, J=14.8 Hz), 7.21-7.35 (5H, m), 7.43 (2H, d, J=8.4 Hz), 7.51-7.61 (4H, m), 7.84 (1H, d, J=14.8 Hz).

5 IR (KBr) 3320, 1666, 1606, 1535, 1335, 831 cm^{-1}

Anal. Calcd. for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_2\text{S} \cdot 0.1\text{H}_2\text{O}$

Calcd. C, 73.46 ; H, 7.44 ; N, 5.71.

Found. C, 73.41 ; H, 7.41 ; N, 5.83.

Working Example 277 (Production of Compound 277)

10 Under nitrogen atmosphere, to a solution of 2-(4-methylphenyl)benzofuran-5-carboxylic acid (200mg) in THF (10ml) were added at room temperature oxalyl chloride (0.1ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated,
15 and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (192mg) and triethylamine (0.22ml), and the mixture was stirred at room temperature for 18 hours. The mixture was added to vigorously stirred water to stop
20 the reaction and extracted with chloroform. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated. The resulting crystals were recrystallized from ethanol to give colorless crystals of
25 2-(4-methylphenyl)-N-[4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl]benzofuran-5-carboxamide (Compound 277) (295.8mg).

m.p. 233-236 °C

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.62-1.83 (4H, m), 2.22 (3H, s), 2.42 (3H, s), 2.57-2.72 (1H, m), 3.32-3.44 (2H, m), 3.59
30 (2H, s), 3.99-4.09 (2H, m), 7.03 (1H, s), 7.31-7.36 (4H, m), 7.56-7.64 (3H, m), 7.76-7.82 (3H, m), 7.87 (1H, s), 8.11 (1H, d, J=1.4 Hz).

IR (KBr) 3388, 2943, 1647, 1597, 1525, 1408, 1319, 1148, 794 cm^{-1}

35 Anal. Calcd. For $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_3$

Calcd. C, 76.63 ; H, 6.65 ; N, 6.16,

Found. C, 76.61 ; H, 6.47 ; N, 6.00.

Working Example 278 (Production of Compound 278)

To a solution of 2-(4-methylphenyl)benzofuran-6-carboxylic acid (200mg) in THF (10ml) were added at room temperature oxalyl chloride (0.1ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (192mg) and triethylamine (0.22ml), and the mixture was stirred at room temperature for 4 hour. The mixture was added to vigorously stirred water to stop the reaction and extracted with dichloromethane. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:4→1:2→2:1) and recrystallized from ethanol to give pale yellow crystals of 2-(4-methylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]benzofuran-6-carboxamide (Compound 278) (280mg).

m.p. 224-227 °C

¹H-NMR (200MHz, CDCl₃) δ 1.41-1.82 (4H, m), 2.22 (3H, s), 2.42 (3H, s), 2.56-2.74 (1H, m), 3.32-3.44 (2H, m), 3.59 (2H, s), 3.98-4.12 (2H, m), 7.02 (1H, s), 7.25-7.37 (4H, m), 7.61-7.66 (3H, m), 7.72-7.81 (3H, m), 7.92 (1H, s), 8.07 (1H, s).

IR (KBr) 3304, 1647, 1520, 1313, 822 cm⁻¹

Anal. Calcd. for C₂₉H₃₀N₂O₃

Calcd. C, 76.63 ; H, 6.65 ; N, 6.16.

Found. C, 76.79 ; H, 6.39 ; N, 6.13.

Working Example 279 (Production of Compound 279)

To a solution of (E)-3-[5-(4-methylphenyl)thiophen-2-yl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]acrylamide (100mg) in DMF (3ml) was added at room temperature methyl iodide (0.5ml), and the mixture was

- stirred for 2 days. Under reduced pressure, the mixture was concentrated, and to the residue was added acetonitrile. The resulting crystals were collected by filtration to give yellow crystals of N,N-dimethyl-N-[4-[[(E)-3-[5-(4-methylphenyl)thiophen-2-yl]-2-propenoyl]amino]benzyl]-4-tetrahydropyranyl ammonium iodide (Compound 279) (101.1mg).
- m.p. 212-216 °C
- ¹H-NMR (200MHz, DMSO-d₆) δ 1.74-1.99 (2H, m), 2.09-2.22 (2H, m), 2.34 (3H, s), 2.87 (6H, br s), 3.24-3.42 (2H, m), 3.48-3.66 (1H, m), 4.00-4.11 (2H, m), 4.46 (2H, s), 6.58 (1H, d, J=15.4 Hz), 7.27 (2H, d, J=7.9 Hz), 7.44-7.58 (4H, m), 7.61 (2H, d, J=7.9 Hz), 7.76 (1H, d, J=15.4 Hz), 7.82 (2H, d, J=8.8 Hz), 10.43 (1H, s).
- IR (KBr) 3165, 1675, 1606, 1525, 1155, 814 cm⁻¹
- Anal. Calcd. for C₂₈H₃₃N₂O₂SI·0.5H₂O
Calcd. C, 56.28 ; H, 5.74 ; N, 4.69.
Found. C, 56.04 ; H, 5.71 ; N, 4.71.
- Working Example 280 (Production of Compound 280)
- To a solution of (E)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-3-[5-(4-isopropylphenyl)thiophen-2-yl]acrylamide (80mg) in DMF (5ml) was added at room temperature methyl iodide (0.04ml), and the mixture was stirred for 3 days. Under reduced pressure, the solvent was evaporated, and to the residue was added acetonitrile. The resulting crystals were collected by filtration to give yellow crystals of N,N-dimethyl-N-[4-[[(E)-3-[5-(4-isopropylphenyl)thiophen-2-yl]-2-propenoyl]amino]benzyl]-4-tetrahydropyranyl ammonium iodide (Compound 280) (76.9mg).
- m.p. 217-220 °C
- ¹H-NMR (200MHz, DMSO-d₆) δ 1.23 (6H, d, J=7.0 Hz), 1.72-2.01 (2H, m), 2.08-2.23 (2H, m), 2.79-3.01 (1H, m), 2.87 (6H, s), 3.25-3.44 (2H, m), 3.49-3.68 (1H, m), 3.99-4.12 (2H, m), 4.46 (2H, s), 6.58 (1H, d, J=15.4 Hz), 7.33 (2H, d J=8.5 Hz), 7.44-7.57 (4H, m), 7.63 (2H, d, J=8.5 Hz), 7.76 (1H,

d, J=15.4 Hz), 7.82 (2H, d, J=8.8 Hz), 10.42 (1H, s).

IR (KBr) 3298, 1654, 1608, 1527, 1452, 1417, 1323, 1252, 1163, 843, 802 cm^{-1}

Anal. Calcd. for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_2\text{SI}$

5 Calcd. C, 58.44 ; H, 6.05 ; N, 4.54.

Found. C, 58.24 ; H, 5.83 ; N, 4.27.

Working Example 281 (Production of Compound 281)

To a solution of 2-(4-methylphenyl)-N-[4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)phenyl]-benzofuran-5-carboxamide (120mg) in DMF (20ml) was added at room temperature methyl iodide (0.04ml), and the mixture was stirred for 24 hours. Under reduced pressure, the solvent was evaporated, and to the residue was added ethanol.

The resulting crystals were collected by filtration to give yellow crystals of N,N-dimethyl-N-[4-[[2-(4-methylphenyl)benzofuran-5-carbonyl]amino]-benzyl]-4-tetrahydropyranyl ammonium iodide (Compound 281) (142.1mg). m.p. 208-212 °C

$^1\text{H-NMR}$ (200MHz, DMSO-d_6) δ 1.71-2.01 (2H, m), 2.12-2.23 (2H, m), 2.39 (3H, s), 2.89 (6H, s), 3.10-3.43 (2H, m), 3.48-3.69 (1H, m), 4.03-4.15 (2H, m), 4.48 (2H, s), 7.36 (2H, d, J=8.0 Hz), 7.53-7.59 (3H, m), 7.77 (1H, d J=8.4 Hz), 7.85-7.99 (5H, m), 8.29 (1H, d, J=1.8 Hz), 10.52 (1H, s).

IR (KBr) 3277, 1643, 1595, 1525, 1468, 1416, 1325, 842, 820, 789, 762 cm^{-1}

Anal. Calcd. for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_3\text{I} \cdot 1.0\text{H}_2\text{O}$

Calcd. C, 58.64 ; H, 5.74 ; N, 4.56.

Found. C, 58.98 ; H, 5.62 ; N, 4.55.

Working Example 282 (Production of Compound 282)

To a solution of 7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) were added at room temperature oxalyl chloride (0.13ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)amino-

- methylaniline (116mg) and triethylamine (0.2ml), and the mixture was stirred at room temperature for 4 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol/diethylether to give pale yellow crystals of 7-(4-methoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 282) (128.5mg).
- m.p. 162-164 °C
- ¹H-NMR (200MHz, CDCl₃) δ 1.61-1.83 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.05-3.10 (2H, m), 3.26-3.44 (4H, m), 3.57 (2H, s), 3.86 (3H, s), 3.96-4.09 (2H, m), 6.98 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.4 Hz), 7.35-7.43 (2H, m), 7.48-7.57 (6H, m), 7.68 (1H, br s).
- IR (KBr) 3332, 1647, 1515, 1248, 818 cm⁻¹
- Anal. Calcd. for C₃₁H₃₄N₂O₃S
Calcd. C, 72.34 ; H, 6.66 ; N, 5.44.
Found. C, 72.25 ; H, 6.67 ; N, 5.43.
- Working Example 283 (Production of Compound 283)
- To a solution of 7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg) in THF (10ml) were added at room temperature oxalyl chloride (0.30ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-(4,4-ethylenedioxycyclohexyl)-N-methylaminomethyl]aniline (0.20g) and triethylamine (0.3ml), and the mixture was stirred at room temperature for 4 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried

with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue solid was recrystallized from acetone/diethylether to give pale yellow crystals of N-[4-[N-(4,4-ethylenedioxy-

5 cyclohexyl)-N-methylaminomethyl]phenyl]-7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 283) (226.4mg).

m.p. 198-201 °C

¹H-NMR (200MHz, CDCl₃) δ 1.45-1.91 (8H, m), 2.21 (3H, s),

10 2.44-2.65 (1H, m), 3.03-3.10 (2H, m), 3.26-3.31 (2H, m), 3.57 (2H, s), 3.86 (3H, s), 3.95 (4H, s), 6.98 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.4 Hz), 7.37-7.43 (2H, m), 7.46-7.60 (6H, m), 7.68 (1H, br s).

IR (KBr) 3359, 1651, 1514, 1252, 1103, 1030, 926, 830 cm⁻¹

15 Anal. Calcd. for C₃₄H₃₈N₂O₄S·0.3H₂O

Calcd. C, 70.88 ; H, 6.75 ; N, 4.86.

Found. C, 70.86 ; H, 6.70 ; N, 4.77.

Working Example 284 (Production of Compound 284)

To a solution of N-[4-[N-(4,4-ethylenedioxy-

20 cyclohexyl)-N-methylaminomethyl]phenyl]-7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (130mg) in THF (15ml) was added at room temperature 6N hydrochloric acid (1ml), and the mixture was stirred for 66 hours. To the mixture was added sodium bicarbonate

25 solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine and magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the resulting solid was recrystallized from ethyl acetate/hexane to give pale yellow crystals of 7-(4-

30 methoxyphenyl)-N-[4-[N-methyl-N-(4-oxocyclohexyl)aminomethyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 284) (78.3mg).

m.p. 133-139 °C

¹H-NMR (200MHz, CDCl₃) δ 1.74-2.19 (4H, m), 2.23 (3H, s),

35 2.30-2.59 (4H, m), 2.81-2.97 (1H, m), 3.04-3.10 (2H, m), 3.26-3.32 (2H, m), 3.60 (2H, s), 3.86 (3H, s), 6.98 (2H,

d, $J=9.2$ Hz), 7.33 (2H, d, $J=8.4$ Hz), 7.38-7.43 (2H, m), 7.48-7.58 (6H, m), 7.71 (1H, br s).

IR (KBr) 3273, 1711, 1651, 1605, 1515, 1408, 1317, 1248, 1180, 820 cm^{-1}

5 Anal. Calcd. for $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_3\text{S}\cdot 0.2\text{H}_2\text{O}$

Calcd. C, 72.48 ; H, 6.54 ; N, 5.28.

Found. C, 72.33 ; H, 6.42 ; N, 5.13.

Working Example 285 (Production of Compound 285)

To a solution of 7-(4-morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) and 1-hydroxybenzotriazole (0.11g) in DMF (5ml) was added at room temperature 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.16g), and the mixture was stirred for 1 hour. To the mixture was added a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (135mg) and triethylamine (0.11ml) in DMF (5ml), and the mixture was stirred for 18 hours. Under reduced pressure, the mixture was concentrated, and to the mixture was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:2) to give yellow crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 285) (113.9mg).

m.p. 255-259 $^{\circ}\text{C}$

$^1\text{H-NMR}$ (200MHz, CDCl_3) δ 1.63-1.84 (4H, m), 2.21 (3H, s), 2.55-2.76 (1H, m), 3.02-3.10 (2H, m), 3.19-3.46 (8H, m), 3.58 (2H, s), 3.85-3.93 (4H, m), 3.98-4.10 (2H, m), 6.99 (2H, d, $J=9.2$ Hz), 7.32 (2H, d, $J=8.4$ Hz), 7.37-7.45 (2H, m), 7.49-7.58 (6H, m), 7.67 (1H, br s).

IR (KBr) 3288, 1653, 1606, 1522, 1232, 1119, 928, 816 cm^{-1}

35 Anal. Calcd. for $\text{C}_{34}\text{H}_{38}\text{N}_4\text{O}_3\text{S}\cdot 0.5\text{H}_2\text{O}$

Calcd. C, 70.56 ; H, 6.97 ; N, 7.26.

Found. C, 70.43 ; H, 6.83 ; N, 7.22.

Working Example 286 (Production of Compound 286)

To a solution of 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) was added at room temperature oxalyl chloride (0.08ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). To the mixture were added at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (112mg) and triethylamine (0.13ml), and the mixture was stirred at room temperature for 18 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give colorless crystals of 7-(3,4-methylenedioxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 286) (183.2mg). m.p. 193-194 °C

¹H-NMR (200MHz, CDCl₃) δ 1.52-1.83 (4H, m), 2.21 (3H, s), 2.54-2.72 (1H, m), 3.04-3.10 (2H, m), 3.23-3.44 (4H, m), 3.57 (2H, s), 3.98-4.09 (2H, m), 6.01 (2H, s), 6.88 (1H, d, J=8.8 Hz), 7.01-7.07 (2H, m), 7.29-7.38 (4H, m), 7.46-7.58 (4H, m), 7.68 (1H, br s).

IR (KBr) 3334, 1647, 1506, 1475, 1408, 1313, 1232, 1041, 818 cm⁻¹

Anal. Calcd. for C₃₁H₃₂N₂O₄S

Calcd. C, 70.43 ; H, 6.10 ; N, 5.30.

Found. C, 70.28 ; H, 5.94 ; N, 5.14.

Working Example 287 (Production of Compound 287)

To a solution of 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (200mg) in THF (10ml) were added at room temperature oxalyl chloride (0.11ml) and a

drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the mixture was concentrated, and the residue was dissolved in THF (20ml). To the mixture was added a solution of added at 0°C 4-[N-(4,4-ethylenedioxy-cyclohexyl)-N-methylaminomethyl]aniline (0.19g) and triethylamine (0.18ml) in THF (5ml), and the mixture was stirred at room temperature for 16 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethyl acetate/ diisopropylether) to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-(4,4-ethylenedioxy-cyclohexyl)-N-methylaminomethyl]-phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 287) (119.1mg). The mother liquor was concentrated to give crude product (91.5mg).
m.p. 172-174 °C

¹H-NMR (200MHz, CDCl₃) δ 1.44 (3H, t, J=7.0 Hz), 1.51-1.88 (8H, m), 2.20 (3H, s), 2.44-2.64 (1H, m), 3.08 (2H, t, J=4.6 Hz), 3.56 (2H, s), 3.95 (4H, s), 4.08 (2H, q, J=7.0 Hz), 4.36 (2H, t, J=4.6 Hz), 6.96 (2H, d, J=9.0 Hz), 7.05 (1H, d, J=8.4 Hz), 7.32 (2H, d, J=8.4 Hz), 7.40-7.56 (8H, m).
IR (KBr) 3350, 1651, 1515, 1493, 1242, 1101, 922, 829, 802 cm⁻¹

Anal. Calcd. for C₃₅H₄₀N₂O₅

Calcd. C, 73.92 ; H, 7.09 ; N, 4.93.

Found. C, 73.82 ; H, 7.01 ; N, 4.90.

Working Example 288 (Production of Compound 288)

To a solution of 7-(4-ethoxyphenyl)-N-[4-[N-(4,4-ethylenedioxy-cyclohexyl)-N-methylaminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (151.5mg) in THF (10ml) was added at room temperature 3N hydrochloric acid (2ml), and the mixture was stirred for 22 hours. To the mixture was added saturated sodium bicarbonate solution,

- and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated to give colorless solid, which was
- 5 recrystallized from ethyl acetate/diisopropylether to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(4-oxocyclohexyl) aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 288) (103.5mg).
- 10 m.p. 146-148 °C
- ¹H-NMR (200MHz, CDCl₃) δ 1.44 (3H, t, J=7.0 Hz), 1.80-2.19 (4H, m), 2.23 (3H, s), 2.29-2.59 (4H, m), 2.83-2.98 (1H, m), 3.04-3.12 (2H, m), 3.61 (2H, s), 4.08 (2H, q, J=7.0 Hz), 4.34-4.39 (2H, m), 6.96 (2H, d, J=8.8 Hz), 7.05 (1H, d, J=8.4
- 15 Hz), 7.33 (2H, d, J=8.0 Hz), 7.41-7.57 (8H, m).
- IR (KBr) 3329, 1709, 1645, 1518, 1495, 1242, 825 cm⁻¹
- Anal. Calcd. for C₃₃H₃₆N₂O₄·0.25H₂O
- Calcd. C, 74.91 ; H, 6.95 ; N, 5.29.
- Found. C, 74.68 ; H, 6.92 ; N, 5.28.
- 20 Working Example 289 (Production of Compound 289)
- To a solution of 4-[1-(4-methylphenylsulfonyl)-piperidin-4-yl]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (200mg) in THF (10ml) were added at room temperature oxalyl chloride (0.08ml) and a drop of DMF, and
- 25 the mixture was stirred for 1 hour. Under reduced pressure, the mixture was concentrated, and the residue was dissolved in THF (20ml). To the mixture was added at 0°C a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-aniline (114mg) and triethylamine (0.2ml) in THF (5ml), and
- 30 the mixture was stirred at room temperature for 3 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the
- 35 residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from

ethanol to give colorless crystals of 4-[1-(4-methyl-phenylsulfonyl)piperidin-4-yl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzocycloheptene-8-carboxamide (Compound 289)

5 (203.5mg).

m.p. 175-176 °C

¹H-NMR (200MHz, CDCl₃) δ 1.66-1.81 (4H, m), 1.83-1.92 (4H, m), 2.04-2.17 (2H, m), 2.21 (3H, s), 2.26-2.43 (3H, m), 2.45 (3H, s), 2.65-2.71 (2H, m), 2.76-2.86 (2H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 3.87-4.10 (4H, m), 6.97-7.13 (3H, m), 7.29-7.37 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.58 (1H, s), 7.68 (2H, d, J=8.2 Hz).

IR (KBr) 3346, 1647, 1518, 1344, 1159, 926, 725, 546 cm⁻¹

15 Anal. Calcd. for C₃₇H₄₅N₃O₄S

Calcd. C, 70.78 ; H, 7.22 ; N, 6.69.

Found. C, 70.71 ; H, 7.14 ; N, 6.46.

Working Example 290 (Production of Compound 290)

In THF (3.4ml) was dissolved 7-(5-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (340mg), and to the mixture were added oxalyl chloride (0.198ml) and DMF (one drop) while stirring at room temperature. The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was removed, and the resulting residue was dissolved in THF (5.1ml). The mixture was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (308mg) and triethylamine (0.473ml) in THF (5.1ml), under ice-cooling, and the mixture was stirred at room temperature for 13 hours. The mixture was poured into water, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=2/1) and recrystallized from hexane/ethyl acetate to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino-

methyl]phenyl]-7-(5-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 290) (20mg).

m.p. 129-130°C

¹H-NMR (200MHz, CDCl₃) δ 1.50-1.82 (4H, m), 2.21 (3H, s), 2.31 (3H, s), 2.65 (1H, m), 3.08 (2H, t, J=4.6Hz), 3.37 (2H, dt, J=11.2, 3.2Hz), 3.58 (2H, s), 4.04 (2H, m), 4.37 (2H, t, J=4.6Hz), 6.92 (1H, d, J=5.2Hz), 7.04 (1H, d, J=5.2Hz), 7.18-7.52 (7H, m), 7.51-7.56 (2H, m)

IR (KBr)

3294, 1653, 1597, 1514, 1498, 1456, 1406, 1315, 1248, 733cm⁻¹

Working Example 291 (Production of Compound 291)

In THF (10ml) was dissolved 7-(3-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (240mg), and to the mixture were added oxalyl chloride (0.15ml) and DMF (one drop) while stirring at room temperature, and the mixture was stirred at room temperature for 1.5 hours. Under reduced pressure, the solvent was removed, and the resulting residue in THF (6ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (247mg) and triethylamine (0.35ml) in THF (10ml), under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The mixture was poured into water, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=2/1) and recrystallized from hexane/ethyl acetate to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(3-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 291) (180mg).

m.p. 194-195°C

¹H-NMR (200MHz, CDCl₃) δ 1.60-1.84 (4H, m), 2.22 (3H, s), 2.69 (1H, m), 3.09 (2H, t, J=4.6Hz), 3.36 (2H, dt, J=11.2, 2.6Hz), 3.60 (2H, s), 4.04 (2H, m), 4.34 (2H, t, J=4.6Hz), 7.03 (1H, d, J=8.4Hz), 7.25-7.42 (7H, m), 7.47 (1H, dd, J=8.4, 2.2Hz), 7.54 (1H, s), 7.58 (1H, s), 7.67 (1H, s)

IR (KBr)

3306, 1645, 1604, 1514, 1496, 1456, 1408, 1321, 1230, 781 cm^{-1}

Anal. Calcd. for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_3\text{S}$

Calcd. C, 70.86; H, 6.37; N, 5.90.

5 Found. C, 70.74; H, 6.16; N, 5.92

Working Example 292 (Production of Compound 292)

In THF 10ml was dissolved in 7-(4-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (250mg), and to the mixture were added oxalyl chloride
10 (0.145ml) and DMF (one drop) while stirring at room temperature, and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was removed, and the resulting residue in methylene chloride (10ml) was added dropwise to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (250mg) and
15 triethylamine (0.35ml) in THF(5ml), under ice-cooling, and the mixture was stirred at room temperature for 13 hours. The mixture was poured into water, extracted with ethyl acetate, washed with saturated brine and dried with
20 magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=2/1) and recrystallized from hexane/ethyl acetate to give N-[4-[N-methyl-N-(tetra-hydropyran-4-yl)aminomethyl]phenyl]-
25 7-(4-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 292) (185mg).

m.p. 147-148°C

^1H -NMR (200MHz, CDCl_3) δ 1.60-1.80 (4H, m), 2.21 (3H, s), 2.31 (3H, s), 2.64 (1H, m), 3.06 (2H, t, $J=4.2\text{Hz}$), 3.37 (2H, dt, $J=11.4, 2.8\text{Hz}$), 3.57 (2H, s), 4.04 (2H, m), 4.33 (2H, t, $J=4.2\text{Hz}$), 6.82 (1H, d, $J=1.2\text{Hz}$), 6.99 (1H, d, $J=8.4\text{Hz}$), 7.04 (1H, d, $J=1.2\text{Hz}$), 7.19 (1H, s), 7.41-7.57 (5H, m), 7.67 (1H, s)
30

IR (KBr) 3292, 1653, 1597, , 1514, 1456, 1406, 1315, 1246, 733 cm^{-1}
35

Anal. Calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_3\text{S} \cdot 0.5\text{H}_2\text{O}$

Calcd. C, 69.99; H, 6.68; N, 5.63.

Found. C, 69.85; H, 6.43; N, 5.68.

Working Example 293 (Production of Compound 293)

In THF (5.0ml) was dissolved 7-(4-fluorophenyl)-
5 2,3-dihydro-1-benzoxepine-4-carboxylic acid (137mg), and
to the mixture were added DMF (one drop) and oxalyl chloride
(0.085ml). The mixture was stirred at room temperature for
1 hour, and the solvent was removed under reduced pressure.
The residue was dissolved in THF (5.0ml), and to the mixture
10 was added a solution of 4-[(N-methyl-N-tetrahydropyran-
4-yl)aminomethyl]aniline (117mg) and triethylamine
(0.135ml) in THF (5.0ml). The mixture was stirred at room
temperature for 1 hour, and to the mixture was added water
(50ml). The mixture was extracted with ethyl acetate (100ml
15 and 50ml), and the organic layer was dried with anhydrous
magnesium sulfate. The solvent was removed under reduced
pressure, and the residue was purified with silica gel column
chromatography and recrystallized to give 7-(4-fluoro-
phenyl)-N-[4-[(N-methyl-N-tetrahydropyran-4-yl)amino-
20 methyl]-phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide
(Compound 293) (149mg, 64%) as pale yellow needle crystals.
mp 177-178 °C.

IR (KBr) 3351, 2938, 1649, 1632, 1595, 1518, 1491, 1412,
1316, 1219, 829cm⁻¹.

25 ¹H NMR (200MHz, CDCl₃) δ 1.69-1.77 (4H, m), 2.21 (3H, s),
2.60-2.70 (1H, m), 3.09 (2H, t, J=4.2Hz), 3.37 (2H, td,
J=11.1, 2.9Hz), 3.58 (2H, s), 4.04 (2H, d, J=10.6Hz), 4.37
(2H, t, J=4.7Hz), 7.04-7.16 (3H, m), 7.29-7.56 (8H, m).
Anal. Calcd. for C₃₀H₃₁FN₂O₃ ; C, 74.05, H, 6.42, N, 5.76.

30 Found ; C, 73.90, H, 6.35, N, 5.53.

Working Example 294 (Production of Compound 294)

To a suspension of 6-(4-methylphenyl)-2H-
thiochromene-3-carboxylic acid (0.36 g, 1.28 mmol) in
dichloromethane (5 ml) were added at 0°C oxalate chloride
35 (0.33 ml, 3.84 mmol) and N,N-dimethylformamide (one drop),
and the mixture was stirred at room temperature for 1 hour.

The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (3 ml). To the mixture was added dropwise a solution of aniline (0.31 g, 1.41 mmol) and triethylamine (0.54 ml, 3.84 mmol) in tetrahydrofuran (2 ml), and the mixture was stirred for 3 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the resulting powder was washed with hexane to give 6-(4-methylphenyl)-N-(4-((N-methyl-N-tetrahydropyran-4-yl)amino)-methyl)phenyl-2H-thiochromene-3-carboxamide (Compound 294) (0.45 g, 72%) as pale yellow powder.

m.p. 200°C.

¹H-NMR (DMSO-d₆) δ: 7.32-7.36 (3H, m), 7.21-7.28 (4H, m), 7.07 (1H, d, J=8.2), 6.92-6.99 (4H, m), 3.50-3.66 (2H, m), 3.48 (2H, s), 3.20 (2H, s), 2.86-3.00 (2H, m), 2.20-2.37 (1H, m), 2.03 (3H, s), 1.78 (3H, s), 1.08-1.46 (4H, m).

Anal. Calcd for C₃₀H₃₂N₂O₂S · 0.25H₂O :

C; 73.66, H; 6.70, N; 5.73.

Found : C; 73.84, H; 6.60, N; 5.84.

Working Example 295 (Production of Compound 295)

To a suspension of 6-(4-methylphenyl)-2H-thiochromene-3-carboxylic acid (226 mg, 0.785 mmol) in tetrahydrofuran (7 ml) were added oxalyl chloride (0.21 ml, 2.35 mmol) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (5ml). To the mixture was added dropwise a solution of (E)-4-((N-(4-hydroxycyclohexyl)-N-methyl)aminomethyl)aniline (202 mg, 0.864 mmol) and triethylamine (0.33 ml, 2.35 mmol) in tetrahydrofuran (2 ml), and the mixture was stirred for 15 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The

solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:ethanol (2:1)] to give (E)-N-(4-((N-(4-hydroxycyclohexyl)-N-methyl)amino) methyl)phenyl-6-(4-methylphenyl)-2H-thiochromene-3-carboxamide (Compound 295) (160 mg, 41%), which was recrystallized from ethyl acetate/hexane to give yellow crystals.

m.p. 149°C

¹H-NMR (CDCl₃) δ: 7.73 (1H, br s), 7.42-7.58 (6H, m), 7.22-7.38 (5H, m), 3.81 (2H, d, J=0.8), 3.59 (2H, s), 3.55-3.68 (1H, m), 2.42-2.61 (1H, m), 2.40 (3H, s), 2.21 (3H, s), 1.86-2.20 (4H, m), 1.23-1.57 (4H, m).

Anal. Calcd for C₃₁H₃₃N₂O₄S · 1.25H₂O:

C; 71.44, H; 7.06, N; 5.37.

Found: C; 71.12, H; 6.53, N; 5.51.

Working Example 296 (Production of Compound 296)

To a suspension of 6-(4-methylphenyl)-2H-thiochromene-3-carboxylic acid (204 mg, 0.708 mmol) in tetrahydrofuran (6 ml) were added oxalyl chloride (0.19 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in tetrahydrofuran (5 ml). To the mixture was added dropwise a solution of 4-((N-(2-methoxy-ethyl)-N-methyl)aminomethyl)aniline (153 mg, 0.802 mmol) and triethylamine (0.30 ml) in tetrahydrofuran (2 ml), and the mixture was stirred for 15 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate.

The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:ethanol (2:1)] to give N-(4-(N-(4-methoxyethyl)-N-methyl)aminomethyl)-phenyl-6-(4-methylphenyl)-2H-thiochromene-3-carboxamide (Compound 296) (170 mg, 52%), which was recrystallized from ethyl acetate/hexane to give yellow crystals.

m.p. 101°C

¹H-NMR (CDCl₃) δ: 7.67 (1H, br s), 7.41-7.57 (6H, m),
7.20-7.38 (5H, m), 3.82 (2H, t, J=0.8), 3.56 (2H, s), 3.53
(2H, t, J=5.8), 3.35 (3H, s), 2.61 (2H, t, J=5.8), 2.40 (3H,
5 s), 2.28 (3H, s).

Anal. Calcd for C₂₈H₃₀N₂O₂S · 0.25H₂O:

C; 72.62, H; 6.64, N; 6.05.

Found: C; 72.43, H; 6.39, N; 6.36.

Working Example 297 (Production of Compound 297)

10 To a suspension of 7-(4-methylphenyl)-2,3-dihydro-
1-benzothiepine-4-carboxylic acid (292 mg, 0.987 mmol) in
tetrahydrofuran (10 ml) were added at 0°C oxalyl chloride
(0.26 ml) and N,N-dimethylformamide (one drop), and the
mixture was stirred at room temperature for 1.5 hours. The
15 solvent was evaporated, and the residue was dissolved in
tetrahydrofuran (8 ml). To the residue was added dropwise
a solution of 4-((N-(3-ethoxycarbonylethyl)-N-methyl)-
aminomethyl)aniline (233 mg, 0.987 mmol) and triethylamine
(0.42 ml) in tetrahydrofuran (2 ml) at 0°C, and the mixture
20 was stirred at room temperature for 17 hours. To the mixture
was added water, and the mixture was extracted with ethyl
acetate. The extract was washed with saturated brine and
dried with magnesium sulfate. The solvent was evaporated,
and the residue was purified with silica gel column
25 chromatography [ethyl acetate] to give N-(4-(N-(3-ethoxy-
carbonylethyl)-N-methyl)aminomethyl)phenyl-7-(4-methyl-
phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide
(Compound 297) (408 mg, 80%), which was recrystallized from
acetone/ethanol to give colorless crystals.

30 m.p. 124°C.

¹H-NMR (CDCl₃) δ: 7.89 (1H, br s), 7.38-7.58 (7H, m),
7.22-7.30 (4H, m), 4.14 (2H, q, J=7.4), 3.48 (2H, s), 3.25
(2H, dt, J=5.4, 1.4) 3.05 (2H, t, J=5.4), 2.74 (2H, t, J=6.8),
2.51 (2H, t, J=6.8), 2.39 (3H, s), 2.19 (3H, s), 1.25 (3H,
35 t, J=7.4).

Anal. Calcd for C₃₁H₃₄N₂O₃S: C; 72.34, H; 6.66, N; 5.44.

Found: C; 72.32, H; 6.43, N; 5.45.

Working Example 298 (Production of Compound 298)

To a suspension of 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (222 mg, 0.750 mmol) in tetrahydrofuran (7 ml) was added at 0°C oxalyl chloride (0.26 ml, 2.97 mmol) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (5 ml). To the residue was added dropwise a solution of aniline (149 mg, 0.825 mmol) and triethylamine (0.31 ml, 2.25 mmol) in tetrahydrofuran (2 ml) at 0°C, and the mixture was stirred at room temperature for 3 days. To the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:methanol:triethylamine (5:1:0.6)] to give N-(4-(N-(2-hydroxyethyl)-N-methylaminomethyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 298) (310 mg, 90%).
m.p. 138°C.

¹H-NMR (CDCl₃) δ: 7.74 (1H, br s), 7.40-7.59 (7H, m), 7.23-7.32 (4H, m), 3.64 (2H, t, J=5.2), 3.58 (2H, s), 3.28 (2H, t, J=5.6), 3.07 (2H, t, J=5.6), 2.62 (2H, t, J=5.2).
Anal. Calcd for C₃₁H₃₄N₂O₃S: C; 72.34, H; 6.66, N; 5.44.

Found: C; 72.32, H; 6.43, N; 5.45.

Working Example 299 (Production of Compound 299)

To a suspension of 6-(4-methylphenyl)-2-pyridine-acrylic acid (160mg, 0.67mmol) in DMF (5ml) were added at 0°C 1-hydroxybenzotriazole (99mg, 0.73mmol), 4-[N-methyl-N-(4-tetrahydropyranyl)aminomethyl]aniline (162mg, 0.74 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (192mg, 1.00mmol), triethylamine (0.28ml, 2.01mmol) and 4-dimethylaminopyridine (10mg) in this order, and the mixture was stirred at room temperature for 17 hours.

The mixture was concentrated under reduced pressure, and to the residue was added ethyl acetate (40ml). The mixture was washed with water (5ml, 3ml×2), saturated sodium bicarbonate solution (3ml×3) and saturated brine (3ml) in this order. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (silica gel 15g, ethyl acetate/methanol=9/1). The desired fraction was concentrated under reduced pressure to give N-[4-
10 [N-methyl-N-(4-tetrahydropyranyl)aminomethyl]phenyl]-6-(4-methylphenyl)-2-pyridineacrylamide (Compound 299) (259mg, 0.59mmol, 88%).

IR (KBr): 1667, 1634, 1601, 1537, 1514 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) δ : 1.55-1.85 (4H, m), 2.21 (3H, s), 2.43 (3H, s), 2.55-2.75 (1H, m), 3.30-3.45 (2H, m), 3.58 (2H, s),
15 3.95-4.10 (2H, m), 7.20-7.50 (5H, m), 7.45-7.85 (6H, m), 7.98 (2H, d, $J=8.2\text{Hz}$).

Working Example 300 (Production of Compound 300)

In DMF(5ml) was dissolved 7-(3,4-methylene-
20 dioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid, and to the mixture were added 1-hydroxybenzotriazole (67mg, 0.50mmol), 4-[N-methyl-N-(4-tetrahydropyranyl)-aminomethyl]aniline (109mg, 0.49mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (130mg,
25 0.68mmol), triethylamine (0.189ml, 1.36mmol) and 4-dimethylaminopyridine (3mg). The mixture was stirred at room temperature for 18 hours and concentrated under reduced pressure. To the residue was added ethyl acetate (60ml), and the mixture was washed with water (5ml×3), saturated sodium
30 bicarbonate solution (3ml×3) and saturated brine (5ml) in this order. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure.

The residue was purified with column chromatography (silica gel 15g, ethyl acetate). The desired fraction was
35 concentrated under reduced pressure, and to the residue was added ethyl acetate. Insoluble materials were filtered,

and the insoluble materials were washed with ethyl acetate and dried under reduced pressure to give 7-(3,4-methylenedioxyphenyl)-N-[4-[N-methyl-N-(4-tetrahydropyranyl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 300) (187mg, 0.36mmol, 81%).
IR (KBr): 1653, 1597, 1514 cm^{-1} .
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.55-1.85 (4H, m), 2.21 (3H, s), 2.55-2.80 (1H, m), 3.00-3.15 (2H, m), 3.30-3.45 (2H, m), 3.58 (2H, s), 3.95-4.15 (2H, m), 4.30-4.45 (2H, m), 6.01 (2H, s), 6.88 (1H, d, $J=8.6\text{Hz}$), 6.95-7.10 (3H, m), 7.20-7.65 (7H, m).
Working Example 301 (Production of Compound 301)

In DMF (6ml) was dissolved 7-morpholino-2,3-dihydro-1-benzoxepine-4-carboxylic acid (200mg, 0.73mmol), and to the mixture were added at 0°C 1-hydroxybenzotriazole (108mg, 0.80mmol), 4-[N-methyl-N-(4-tetrahydropyranyl)aminomethyl]aniline (176mg, 0.80mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (209mg, 1.09mmol), triethylamine (0.304ml, 2.18mmol) and 4-dimethylaminopyridine (3mg). The mixture was stirred at room temperature for 13 hours and concentrated under reduced pressure. To the residue was added ethyl acetate (40ml), and the mixture was washed with water (5ml \times 3), saturated sodium bicarbonate solution (5ml \times 3) and saturated brine (5ml) in this order. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 15g, ethyl acetate/methanol=1/0 \rightarrow 9/1). The desired fraction was concentrated under reduced pressure, and to the residue was added diethylether. Insoluble materials were filtered, and the insoluble materials were washed with diethylether and dried under reduced pressure to give N-[4-[N-methyl-N-(4-tetrahydropyranyl)aminomethyl]phenyl]-7-morpholino-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 301) (248mg, 0.52mmol, 71%).
IR (KBr): 1655, 1597, 1507 cm^{-1} .

¹H-NMR (CDCl₃) δ: 1.5-1.85 (4H, m), 2.21 (3H, s), 2.55-2.75 (1H, m), 3.0-3.15 (6H, m), 3.3-3.45 (2H, m), 3.57 (2H, s), 3.8-3.9 (4H, m), 3.95-4.1 (2H, m), 4.29 (2H, t, J=4.7Hz), 6.8-7.0 (3H, m), 7.15-7.35 (3H, m), 7.5-7.6

5 (2H+1H(amide-H), m).

Working Example 302 (Production of Compound 302)

In DMF (6ml) was dissolved 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (140mg, 0.50 mmol), and to the mixture were added at 0°C 1-hydroxy-
10 benzotriazole (74mg, 0.55mmol), 4-[N-(2-pyrimidinyl)-aminomethyl]aniline (100mg, 0.50mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (144mg, 0.75mmol). The mixture was stirred at room temperature for 22 hours and concentrated under reduced pressure. To the
15 residue was added ethyl acetate (40ml), and the mixture was washed with water (5ml), saturated sodium bicarbonate solution (5ml×3) and saturated brine (5ml) in this order. The organic layer was dried with anhydrous sodium sulfate and concentrated to about 3ml under reduced pressure.
20 Precipitated insoluble materials were filtered and the insoluble materials were washed with ethyl acetate and dried under reduced pressure to give N-[4-[N-(2-pyrimidinyl)-aminomethyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 302) (129mg, 0.28mmol,
25 56%).

IR (KBr): 1647, 1591, 1518 cm⁻¹.

¹H-NMR (DMSO-d₆) δ: 2.34 (3H, s), 2.9-3.05 (2H, m), 4.2-4.35 (2H, m), 4.46 (2H, d, J=6.6Hz), 6.57 (1H, t, J=4.8Hz), 7.04 (1H, d, J=8.4Hz), 7.2-7.35 (5H, m), 7.5-7.75 (7H, m), 8.27
30 (2H, d, J=4.8Hz), 9.91 (1H, s).

Working Example 303 (Production of Compound 303)

To a mixture of 7-(2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (180mg, 0.66 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-
35 aniline (160mg, 0.73mmol), 1-hydroxybenzotriazole (98mg, 0.73mmol) and DMF (10ml) were added at 0°C 1-[3-(dimethyl-

amino)propyl]-3-ethylcarbodiimide hydrochloride (190mg, 0.99mmol) and triethylamine (0.276ml, 1.98mmol), and the mixture was stirred at room temperature for 24 hours. The mixture was concentrated under reduced pressure, and to the residue was added ethyl acetate (40ml). The mixture was washed with saturated sodium bicarbonate solution (5ml \times 3) and saturated brine (5ml) in this order. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (silica gel 15g, ethyl acetate). The desired fraction was concentrated under reduced pressure, and to the residue was added ethyl acetate. Insoluble materials were filtered, and the insoluble materials were washed with ethyl acetate and dried under reduced pressure to give 7-(2-methyl-1H-tetrazol-5-yl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 303) (217mg, 0.46 mmol, 69%).

IR (KBr): 1647, 1628, 1611, 1595, 1522 cm^{-1} .

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.8 (4H, m), 2.10 (3H, s), 2.4-2.7 (1H, m), 2.9-3.1 (2H, m), 3.15-3.4 (2H, m), 3.52 (2H, s), 3.8-4.0 (2H, m), 4.25-4.45 (2H, m), 4.42 (3H, s), 7.16 (1H, d, $J=8.4\text{Hz}$), 7.26 (2H, d, $J=8.4\text{Hz}$), 7.40 (1H, s), 7.66 (2H, d, $J=8.4\text{Hz}$), 7.92 (1H, dd, $J=1.9, 8.4\text{Hz}$), 8.19 (1H, d, $J=1.9\text{Hz}$).

Working Example 304 (Production of Compound 304)

To a mixture of 7-(1-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (69mg, 0.25 mmol), 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (61mg, 0.28mmol), 1-hydroxybenzotriazole (38mg, 0.28mmol) and DMF (4ml) were added at 0°C 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (97mg, 0.51mmol) and triethylamine (0.106ml, 0.76mmol), and the mixture was stirred at room temperature for 2 days. The mixture was concentrated under reduced pressure, and to the residue was added ethyl acetate. The mixture was washed

- with saturated sodium bicarbonate solution. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 10g, ethyl acetate). The desired fraction was concentrated under reduced pressure, and to the residue was added ethyl acetate. Insoluble materials were filtered and the insoluble materials were washed with ethyl acetate and dried under reduced pressure to give 7-(1-methyl-1H-tetrazol-5-yl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 304) (84mg, 0.18mmol, 70%).
- IR (KBr): 1649, 1630, 1597, 1518 cm^{-1} .
- $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.8 (4H, m), 2.10 (3H, s), 2.45-2.7 (1H, m), 2.95-3.1 (2H, m), 3.15-3.4 (2H, m), 3.51 (2H, s), 3.8-4.0 (2H, m), 4.20 (3H, s), 4.3-4.45 (2H, m), 7.22 (1H, d, $J=8.4\text{Hz}$), 7.26 (2H, d, $J=8.6\text{Hz}$), 7.35 (1H, s), 7.64 (2H, d, $J=8.6\text{Hz}$), 7.76 (1H, dd, $J=2.2, 8.4\text{Hz}$), 7.99 (1H, d, $J=2.2\text{Hz}$).
- 20 Working Example 305 (Production of Compound 305)
- In DMF (12.0ml) was dissolved 1-methyl-7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxazepine-4-carboxylic acid hydrochloride (386mg), and to the mixture was added thionyl chloride (0.26ml). The mixture was stirred at room temperature for 30 minutes, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (10.0ml). Thus prepared acid chloride solution was added dropwise at 0°C to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (310mg) and triethylamine (0.82ml) in dichloromethane (4.0ml). The mixture was stirred at 0°C for 10 minutes and then at room temperature for 22 hours. To the mixture was added water (100ml), and the mixture was extracted with dichloromethane (100ml; twice). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was

purified with silica gel column chromatography (75g, ethyl acetate:ethanol=9:1) and recrystallized from ethanol to give 1-methyl-7-(4-methylphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (Compound 305) (250mg, 43%).
mp 178-181°C.

¹H NMR (200MHz, CDCl₃) δ 1.64-1.76 (4H, m), 2.21 (3H, s), 2.38 (3H, s), 2.66 (1H, septet, J=5.3Hz), 2.96 (2H, t, J=4.4Hz), 3.09 (3H, s), 3.30-3.43 (2H + 2H, m), 3.58 (2H, s), 4.01-4.06 (2H, m), 6.88 (1H, d, J=8.6Hz), 7.23 (2H, d, J=8.0Hz), 7.30 (2H, d, J=8.4Hz), 7.42, (1H, s), 7.461 (2H, d, J=8.2Hz), 7.466 (1H, dd, J=8.3, 2.3Hz), 7.535 (2H, d, J=8.4Hz), 7.539 (1H, d, J=2.6Hz), 7.58 (1H, s).

IR (KBr) 3337, 2949, 2851, 1653, 1516, 1501, 1341, 1304, 1238, 818, 521 cm⁻¹.

Anal. Calcd. for C₃₂H₂₇N₃O₂: C, 77.54; H, 7.52; N, 8.48.

Found: C, 77.51; H, 7.43; N, 8.44.

Working Example 306 (Production of Compound 306)

In water:ethanol:toluene (1:1:10, 18.0ml) were dissolved 4-ethoxyphenyl borate (252mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (613mg), and to the mixture was added potassium carbonate (420mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis-triphenylphosphine palladium (59mg). Under argon atmosphere, the mixture was refluxed for 17 hours. The mixture was diluted with ethyl acetate (200ml) and washed with water (50ml) and saturated brine (50ml). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (75g, ethyl acetate:ethanol=9:1) and recrystallized from ethanol to give 7-(4-ethoxyphenyl)-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (Compound 306) (230mg, 35%).

mp 150.5-152°C.

¹H NMR (200MHz, CDCl₃) δ 1.44 (3H, t, J=7.0Hz), 1.64-1.77 (4H, m), 2.21 (3H, s), 2.57-2.72 (1H, m), 2.96 (2H, t, J=4.5Hz), 3.08 (3H, s), 3.31-3.43 (2H + 2H, m), 3.57 (2H, s), 4.01-4.09 (2H, m), 4.07 (2H, q, J=7.0Hz), 6.88 (1H, d, J=8.4Hz), 6.95 (2H, d, J=8.8Hz), 7.30 (2H, d, J=8.6Hz), 7.40-7.55 (1H + 1H + 1H + 1H, concealed under 7.45 and 7.53), 7.47 (2H, d, J=9.0Hz), 7.53 (2H, d, J=8.8Hz).
IR (KBr) 3372, 2955, 2847, 1680, 1605, 1595, 1518, 1503, 1314, 1240, 1194, 812 cm⁻¹.

Anal. Calcd. for C₂₃H₂₃N₃O₃·0.5H₂O: C, 74.13; H, 7.54; N, 7.86.
Found: C, 74.34; H, 7.31; N, 7.96.

Working Example 307 (Production of Compound 307)

In water:ethanol:toluene (1:1:10, 18.0ml) were dissolved 4-ethylphenyl borate (227mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (611mg), and to the mixture was added potassium carbonate (418mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis-triphenylphosphine palladium (59mg). Under argon atmosphere, the mixture was refluxed for 17 hours, and the mixture was diluted with ethyl acetate (200ml) and washed with water (50ml) and saturated brine (50ml). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (75g, ethyl acetate:ethanol=9:1) and recrystallized from ethanol to give 7-(4-ethylphenyl)-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (Compound 307) (252mg, 39%).
mp 164-165°C.

¹H NMR (200MHz, CDCl₃) δ 1.27 (3H, t, J=7.6Hz), 1.66-1.76 (4H, m), 2.21 (3H, s), 2.54-2.70 (1H, m), 2.69 (2H, q, J=7.7Hz), 2.96 (2H, t, J=4.7Hz), 3.09 (3H, s), 3.29-3.43 (4H, m), 3.57 (2H, s), 4.01-4.06 (2H, m), 6.89 (1H, d,

J=8.6Hz), 7.26 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.8Hz), 7.40 (1H, s), 7.48 (1H, dd, J=8.6, 2.2Hz), 7.49 (2H, d, J=9.2Hz), 7.54 (2H, d, J=8.8Hz), 7.55 (1H, d, J=2.2Hz), 1H was concealed under 7.40-7.56.

5 IR (KBr) 3364, 2946, 2851, 1653, 1514, 1341, 1304, 1233, 1188, 824, 575, 519 cm^{-1} .

Anal. Calcd. for $\text{C}_{33}\text{H}_{33}\text{N}_3\text{O}_2$: C, 77.76; H, 7.71; N, 8.24.

Found: C, 77.81; H, 7.64; N, 8.27.

Working Example 308 (Production of Compound 308)

10 In water:ethanol:toluene (1:1:10, 18.0ml) were dissolved 4-trifluorophenyl borate (190mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)-amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (403mg), and to the mixture was added potassium

15 carbonate (276mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (39mg). Under argon atmosphere, the mixture was refluxed for 17 hours, and the mixture was diluted with ethyl acetate (200ml) and washed

20 with water (50ml) and saturated brine (50ml). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (75g, ethyl acetate: ethanol=9:1) and recrystallized from ethanol

25 to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]-methyl]phenyl]-7-(4-trifluoromethylphenyl)-2,3-dihydro-1-benzoazepine-4-carboxamide (Compound 308) (177mg, 39%).

mp 187.5-188.5°C.

30 ^1H NMR (200MHz, CDCl_3) δ 1.69-1.77 (4H, m), 2.21 (3H, s), 2.57-2.72 (1H, m), 2.98 (2H, t, J=4.6Hz), 3.12 (3H, s), 3.37 (2H, td, J=11.2, 3.3Hz), 3.38 (2H, t, J=4.7Hz), 3.57 (2H, s), 4.01-4.06 (2H, m), 6.91 (1H, d, J=8.4Hz), 7.30 (2H, d, J=8.4Hz), 7.42 (1H, s), 7.49 (1H, dd, J=8.4, 2.2Hz), 7.54

35 (2H, d, J=8.4Hz), 7.55 (1H, s), 7.58 (1H, d, J=2.2Hz), 7.66 (4H, s).

IR (KBr) 2949, 2847, 1651, 1603, 1516, 1325, 1163, 1115, 1073, 847, 812 cm^{-1} .

Anal. Calcd. for $\text{C}_{32}\text{H}_{33}\text{F}_3\text{N}_3\text{O}_2$: C, 69.93; H, 6.24; N, 7.65.
Found: C, 69.66; H, 6.20; N, 7.71.

5 Working Example 309 (Production of Compound 309)

In water:ethanol:toluene (1:1:10, 18.0ml) were dissolved 4-(4-morpholino)phenyl borate (208mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (406mg), and to the mixture was added potassium carbonate (278mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (39mg). Under argon atmosphere, the mixture was refluxed for 17 hours, and the mixture was diluted with ethyl acetate (200ml) and washed with water (50ml) and saturated brine (50ml). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (75g, ethyl acetate:ethanol=9:1) and recrystallized from ethanol to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-pyran-4-yl)amino]methyl]phenyl]-[4-(4-morpholino)-phenyl]-2,3-dihydro-1-benzoazepine-4-carboxamide (Compound 309) (247mg, 52%).

25 mp 209-211°C.

^1H NMR (200MHz, CDCl_3) δ 1.64-1.77 (4H, m), 2.21 (3H, s), 2.57-2.75 (1H, m), 2.96 (2H, t, $J=5.2\text{Hz}$), 3.09 (3H, s), 3.20 (2H, t, $J=4.8\text{Hz}$), 3.18-3.22 (2H, m), 3.33-3.43 (4H, m), 3.58 (2H, s), 3.89 (4H, t, $J=4.8\text{Hz}$), 4.01-4.06 (2H, m), 6.88 (1H, d, $J=8.4\text{Hz}$), 6.97 (2H, d, $J=8.8\text{Hz}$), 7.30 (2H, d, $J=8.8\text{Hz}$), 7.41-7.56 (8H, m).

IR (KBr) 2953, 2847, 1653, 1607, 1514, 1505, 1311, 1232, 1119, 926, 814, 735 cm^{-1} .

Anal. Calcd. for $\text{C}_{35}\text{H}_{42}\text{N}_4\text{O}_5$: C, 74.18; H, 7.47; N, 9.89.

35 Found: C, 74.17; H, 7.39; N, 9.98.

Reference Example 187

In 1,2-dichloroethane (50ml) were suspended p-nitro-benzylaminehydrochloride (3.77g), 4H-tetrahydropyran-4-one (2g) and triethylamine (2.8ml), and to the mixture was added, under ice-cooling, triacetoxy sodium boron hydride (5.92g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 4 hours, and to the mixture were added, under ice-cooling, acetaldehyde (1.5ml) and triacetoxy sodium boron hydride (5.92g). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was neutralized with sodium hydroxide solution. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give N-(4-nitrobenzyl)-N-(tetrahydropyran-4-yl)ethylamine (4.0g) as yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.01 (3H, t, $J=6.9\text{Hz}$), 1.52-1.73 (4H, m), 2.59 (2H, q, $J=6.9\text{Hz}$), 2.68-2.83 (1H, m), 3.34 (2H, dt, $J=3.6, 11.2\text{Hz}$), 3.73 (2H, s), 3.99-4.06 (2H, m), 7.54 (2H, d, $J=9.0\text{Hz}$), 8.16 (2H, d, $J=9.0\text{Hz}$).

IR(neat) ν : 2951, 2841, 1599, 1520 cm^{-1} .

Reference Example 188

In acetic acid (100ml) was dissolved N-(4-nitrobenzyl)-N-(tetrahydropyran-4-yl)ethylamine (4.0g), and to the mixture was added reduced iron (4.2g). The mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitates were filtered off, and the filtrate was washed with sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give 4-(N-ethyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (2.3g) as red oil.

¹H-NMR(δ ppm, CDCl₃) 1.00 (3H, t, J=7.1Hz), 1.52-1.70 (4H, m), 2.54 (2H, q, J=7.1Hz), 2.66-2.82 (1H, m), 3.26-3.39 (2H, m), 3.52 (2H, s), 3.59 (2H, br), 3.95-4.04 (2H, m), 6.64 (2H, d, J=8.5Hz), 7.12 (2H, d, J=8.5Hz).

5 Reference Example 189

In 1,2-dichloroethane (75ml) were suspended p-nitro-benzaldehyde (5g) and 2-amino-1,3-propanediol (3.0g), and to the mixture was added, under ice-cooling, triacetoxysodium boron hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 3.5 hours. To the mixture were added, under ice-cooling, 37% formalin (3ml) and triacetoxysodium boron hydride (9.8g), and the mixture was stirred, under nitrogen atmosphere, at room temperature overnight. To the mixture was added water, and the mixture was concentrated. The residue was neutralized with sodium hydroxide solution, saturated with sodium hydrochloride and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column (ethyl acetate) to give 2-(N-methyl-N-(4-nitro-benzyl)amino)-1,3-propanediol (3.0g) as pale yellow crystals. mp 65-66°C.

¹H-NMR(δ ppm, CDCl₃) 2.31 (3H, s), 2.93-3.06 (1H, m), 3.64-3.80 (4H, m), 3.92 (2H, s), 7.49 (2H, d, J=8.8Hz), 8.20 (2H, d, J=8.8Hz).

IR(KBr) ν: 3349, 2942, 2884, 1520cm⁻¹.

Anal. Calcd. for C₁₁H₁₆N₂O₄: C, 54.99; H, 6.71; N, 11.66.

Found: C, 55.14; H, 6.61; N, 11.55.

30 Reference Example 190

In ethanol (50ml) was dissolved 2-(N-methyl-N-(4-nitrobenzyl)amino)-1,3-propanediol (2.9g), and catalytic reduction was carried out with 5% palladium carbon (0.15g) at room temperature for 2 hours. The catalyst was filtered off, and the solvent of the filtrate was evaporated. The residue was purified with silica gel column (methanol/

triethylamine/ethyl acetate) to give 2-(N-(4-aminobenzyl)-N-methylamino)-1,3-propanediol (0.6g) as pale yellow amorphous.

¹H-NMR(δ ppm, CDCl₃) 2.26 (3H, s), 2.37 (2H, br), 2.91-2.99 (1H, m), 3.55-3.73 (6H, m), 6.65 (2H, d, J=8.4Hz), 7.08 (2H, d, J=8.4Hz).

IR(KBr) ν: 3347, 2942, 2880, 1615cm⁻¹.

Anal. Calcd. for C₁₁H₁₈N₂O₂·0.1H₂O:

C, 62.30; H, 8.65; N, 13.21.

10 Found: C, 62.37; H, 8.79; N, 13.24.

Reference Example 191

In 1,2-dichloroethane (50ml) were suspended p-nitrobenzaldehyde (5g), sarcosine methyl ester hydrochloride (4.6g) and triethylamine (4.6ml), and to the mixture was added, under ice-cooling, triacetoxysodium boron hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 4 hours. To the mixture was added water, and the mixture was concentrated, neutralized with sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give N-(4-nitrobenzyl)sarcosine methyl ester (6.3g) as colorless oil.

¹H-NMR(δ ppm, CDCl₃) 2.39 (3H, m), 3.33 (2H, s), 3.73 (3H, s), 3.80 (2H, s), 7.55 (2H, d, J=8.8Hz), 8.19 (2H, d, J=8.8Hz).

IR(neat) ν: 2951, 2847, 1748cm⁻¹.

30 Reference Example 192

In acetic acid (100ml) was dissolved N-(4-nitrobenzyl)sarcosine methyl ester (5.96g), and to the mixture was added little by little reduced iron (7g). The mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitates were filtered off, and the filtrate was washed

with sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give N-(4-aminobenzyl)sarcosine methyl ester (3.0g) as red oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.36 (3H, m), 3.22 (2H, s), 3.55 (2H, s), 3.65 (2H, br), 3.70 (3H, s), 6.65 (2H, d, $J=8.6\text{Hz}$), 7.11 (2H, d, $J=8.6\text{Hz}$).

IR(neat) ν : 3364, 2949, 1744 cm^{-1} .

Reference Example 193

In 1,2-dichloroethane (50ml) were dissolved p-nitro-benzaldehyde (5g) and 3-methoxypropylamine (3.1g), and to the mixture was added, under ice-cooling, triacetoxysodium boron hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 3 hours, and to the mixture were added, under ice-cooling, 37% formalin (3ml) and triacetoxysodium boron hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 3 hours, and to the mixture was added water. The mixture was concentrated, neutralized with sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and subjected to back extraction with 1N hydrochloric acid. The aqueous layer was washed with ethyl acetate, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give N-(3-methoxypropyl)-N-methyl-4-nitrobenzylamine (5.6g) as yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.72-1.85 (2H, m), 2.20 (3H, s), 2.47 (2H, t, $J=7.3\text{Hz}$), 3.33 (3H, s), 3.43 (2H, t, $J=6.4\text{Hz}$), 3.58 (2H, s), 7.50 (2H, d, $J=9.0\text{Hz}$), 8.18 (2H, d, $J=9.0\text{Hz}$).
IR(neat) ν : 2805, 1605, 1520 cm^{-1} .

Reference Example 194

In acetic acid (70ml) was dissolved N-(3-methoxy-

propyl)-N-methyl-4-nitrobenzylamine (5.5g), and to the mixture was added little by little reduced iron (6.4g). The mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added ethyl acetate. The precipitates were filtered off, the filtrate was washed with sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-((N-3-methoxypropyl-N-methyl)amino-methyl)aniline (4.4g) as red oil.

¹H-NMR(δ ppm, CDCl₃) 1.71-1.85 (2H, m), 2.16 (3H, s), 2.42 (2H, t, J=7.4Hz), 3.32 (3H, s), 3.37 (2H, s), 3.41 (2H, t, J=6.6Hz), 3.61 (2H, br), 6.64 (2H, d, J=8.4Hz), 7.08 (2H, d, J=8.4Hz).

IR(neat) ν: 2946, 2795, 1615cm⁻¹.

Reference Example 195

In ethanol (50ml) was dissolved 7-(4-methylphenyl)-2,3,4,5-tetrahydro-1-benzoxepin-5-one (1g), and to the mixture was added, under ice-cooling, sodium boron hydride (0.3g). The mixture was stirred at room temperature for 30 minutes, and to the mixture was added water. The mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water and concentrated. The residue was dissolved in bis(2-methoxyethyl)ether (20ml), and to the mixture was added hydrochloric acid (5ml). The mixture was stirred at 75°C for 1 hour, poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the precipitated 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine (0.78g) was filtered with hexane to give colorless crystals.

mp 98-100°C.

¹H-NMR(δ ppm, CDCl₃) 2.38 (3H, s), 2.65-2.74 (2H, m), 4.27 (2H, t, J=4.9Hz), 6.01 (1H, dt, J=11.7, 4.4Hz), 6.39 (1H, d, J=11.7Hz), 7.01 (1H, d, J=8.0Hz), 7.23 (2H, d, J=8.2Hz),

7.31-7.38 (2H, m), 7.45 (2H, d, $J=8.0\text{Hz}$).

IR(KBr) ν : 3025, 1491 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}$: C, 86.41; H, 6.82.

Found: C, 86.17; H, 6.61.

5 Reference Example 196

Under ice-cooling, to dimethylformamide (0.2ml) was added dropwise sulfonyl chloride (0.17ml), and the mixture was stirred, under nitrogen atmosphere, at room temperature for 10 minutes. To the mixture was added 7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine (0.3g), and the mixture was stirred, under nitrogen atmosphere, at 90°C for 3 hours. To the mixture was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-sulfonylchloride (0.36g) as pale yellow crystals. mp 162-166°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.40 (3H, s), 3.27 (2H, t, $J=4.7\text{Hz}$), 4.41 (2H, t, $J=4.7\text{Hz}$), 7.11 (1H, d, $J=9.6\text{Hz}$), 7.26 (2H, d, $J=8.2\text{Hz}$), 7.44 (2H, d, $J=8.2\text{Hz}$), 7.57-7.62 (2H, m), 7.70 (1H, s).

IR(KBr) ν : 3027, 1634, 1493 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{ClO}_2\text{S}$: C, 60.98; H, 4.52.

Found: C, 61.14; H, 4.26.

25 Reference Example 197

Under argon atmosphere, a solution of ethyl (E)-3-(5-bromothiophen-2-yl)acrylate (1.00g), 4-isopropylphenyl borate (0.86g) and potassium carbonate (1.12g) in toluene/ethanol/water (40/4/4ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine) palladium (0.14g), and the mixture was refluxed for 18 hours and then cooled to room temperature. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was

purified with column chromatography (ethyl acetate/hexane=1:9) to give pale yellow crystals of methyl (E)-3-[5-(4-isopropylphenyl)-thiophen-2-yl]acrylate (0.83g).

m.p. 117-119 °C

5 ¹H-NMR (200MHz, CDCl₃) δ 1.27 (6H, d, J=6.8 Hz), 2.94-3.00 (1H, m), 3.80 (3H, s), 6.22 (1H, d, J=15.8 Hz), 7.24-7.28 (4H, m), 7.54 (2H, d, J=7.8 Hz), 7.76 (1H, d, J=15.8 Hz). IR (KBr) 1718, 1622, 1436, 1306, 1230, 1203, 1165, 806 cm⁻¹. Anal. Calcd. for C₁₇H₁₈O₂S

10 Calcd. C, 71.30 ; H, 6.33 ; S, 11.20.

Found. C, 71.22 ; H, 6.33 ; S, 11.23.

Reference Example 198

To a solution of methyl (E)-3-[5-(4-isopropylphenyl)-thiophen-2-yl]acrylate (0.75mg) in THF/ethanol (10/10ml) 15 was added at room temperature 2N sodium hydroxide solution (2.0ml), and the mixture was stirred for 20 hours. Under reduced pressure, the mixture was concentrated, and to the residue was added 1N hydrochloric acid (10ml). The mixture was extracted with ethyl acetate, and the organic layer was 20 washed with saturated brine, dried with magnesium sulfate and concentrated. The resulting crystals were collected by filtration to give pale yellow crystals of (E)-3-[5-(4-isopropylphenyl)thiophen-2-yl]acrylic acid (639.7mg). m.p. 216-219 °C

25 ¹H-NMR (200MHz, CDCl₃) δ 1.28 (6H, d, J=7.0 Hz), 2.86-3.01 (1H, m), 6.22 (1H, d, J=15.7 Hz), 7.23-7.33 (4H, m), 7.56 (2H, d, J=8.4 Hz), 7.85 (1H, d, J=15.7 Hz).

IR (KBr) 2966, 1668, 1608, 1414, 1302, 1263, 1228, 804 cm⁻¹. Anal. Calcd. for C₁₆H₁₆O₂S

30 Calcd. C, 70.56 ; H, 5.92 ; S, 11.77.

Found. C, 70.23 ; H, 5.94 ; S, 11.62.

Reference Example 199

Under argon atmosphere, a solution of methyl (E)-3-(5-bromothiophen-2-yl)acrylate (0.23g), 4-tert-butyl- 35 phenyl borate (0.3g) and potassium carbonate (0.26g) in toluene/ethanol/water (20/2/2ml) was stirred at room

temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine) palladium (32mg), and the mixture was refluxed for 18 hours and then cooled to room temperature. To the organic layer was added ethyl acetate, and the mixture was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:9) to give pale yellow crystals of methyl (E)-3-[5-(4-tert-butylphenyl)thiophen-2-yl]acrylate (240mg). This compound was used for the following reaction, without subjecting further purification.

¹H-NMR (200MHz, CDCl₃) δ 1.34 (9H, s), 3.80 (3H, s), 6.22 (1H, d, J=15.8 Hz), 7.21-7.30 (2H, m), 7.42 (2H, d, J=8.7 Hz), 7.55 (2H, d, J=8.7 Hz), 7.76 (1H, d, J=15.8 Hz). IR (KBr) 1716, 1622, 1436, 1302, 1232, 1207, 1165, 972, 806 cm⁻¹

Reference Example 200

To a solution of methyl (E)-3-[5-(4-tert-butylphenyl)-thiophen-2-yl]acrylate (190mg) of THF/ethanol (15/15ml) was added at room temperature 2N sodium hydroxide solution (2.0ml), and the mixture was stirred 18 hours. To the mixture was added 1N hydrochloric acid (5ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the precipitated crystals were collected by filtration, which were washed with hexane to give yellow crystals of (E)-3-[5-(4-tert-butylphenyl)thiophen-2-yl]acrylic acid (149.7mg). This compound was used for the following reaction, without subjecting further purification.

¹H-NMR (200MHz, CDCl₃) δ 1.35 (9H, s), 6.22 (1H, d, J=15.6 Hz), 7.20-7.29 (2H, m), 7.43 (2H, d, J=8.8 Hz), 7.56 (2H, d, J=8.8 Hz), 7.85 (1H, d, J=15.6 Hz). IR (KBr) 2962, 1678, 1612, 1414, 1302, 1232, 806 cm⁻¹

Reference Example 201

To a solution of 4'-methylacetophenone (10.0g) in ethanol (100ml) were added at room temperature an aqueous solution (50ml) of hydroxyamine hydrochloride (7.77g) and sodium acetate (9.63g), and the mixture was refluxed for 24 hours and then cooled. The mixture was concentrated, and to the residue was added 1N hydrochloric acid (150ml). The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:3) to give colorless crystals of 4'-methylacetophenonoxime (10.89g).

¹H-NMR (200MHz, CDCl₃) δ 2.28 (3H, s), 2.37 (3H, s), 7.19 (2H, d, J=8.1 Hz), 7.53 (2H, d, J=8.1 Hz), 8.55-8.69 (1H, m).
Reference Example 202

To a solution of 4'-methylacetophenonoxime (10.46g) in DMF (250ml) was added at 0°C sodium hydride (60%, 3.08g), and the mixture was stirred at room temperature for 1 hour. To the mixture was added a solution of 4-fluorobenzaldehyde (9.57g) in THF (300ml), and the mixture was stirred for 5 days. To the mixture was added 1N hydrochloric acid (200ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:5) to give colorless crystals of 4-(4'-methyl-α-methylbenzylidene-aminoxy)benzaldehyde (11.23g).

m.p. 96-98 °C

¹H-NMR (200MHz, CDCl₃) δ 2.41 (3H, s), 2.47 (3H, s), 7.25 (2H, d, J=7.8 Hz), 7.43 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=7.8 Hz), 7.88 (2H, d, J=8.8 Hz), 9.93 (1H, s).

IR (KBr) 1699, 1597, 1576, 1498, 1232, 1207, 1149, 916, 820 cm⁻¹

Anal. Calcd. for C₁₆H₁₅NO₂

Calcd. C, 75.87 ; H, 5.97 ; N, 5.53.

Found. C, 75.73 ; H, 6.04 ; N, 5.48.

Reference Example 203

5 A solution of 4-(4'-methyl- α -methylbenzylidene-
aminoxy)benzaldehyde (5.0g) in 1N hydrochloric acid/acetic
acid (80ml) was stirred at 100-110°C for 24 hours and then
cooled to room temperature. To the mixture was added water,
and the mixture was extracted with ethyl acetate. The
organic layer was washed with saturated brine and dried with
10 magnesium sulfate. Under reduced pressure, the mixture was
concentrated, and the residue was purified with column
chromatography (ethyl acetate/hexane=1:9) to give
colorless crystals of 2-(4-methylphenyl)benzofuran-5-
aldehyde (1.50g).

15 m.p. 162-164 °C

¹H-NMR (200MHz, CDCl₃) δ 2.41 (3H, s), 7.06 (1H, s), 7.28
(2H, d, J=8.0 Hz), 7.62 (1H, d, J=8.4 Hz), 7.77 (2H, d, J=8.0
Hz), 7.84 (1H, dd, J=8.4, 1.8 Hz), 8.11 (1H, d, J=1.8 Hz),
10.06 (1H, s).

20 IR (KBr) 1697, 1292, 1271, 824, 798 cm⁻¹

Anal. Calcd. For C₁₆H₁₂O₂

Calcd. C, 81.34 ; H, 5.12.

Found. C, 81.21 ; H, 5.11.

Reference Example 204

25 To a solution of 2-(4-methylphenyl)benzofuran-5-
carbaldehyde (500mg) and 1-methylcyclohexene (1.2ml) in DMF
(15ml) was added a solution (9ml) of sodium chlorite (80%,
1.5g) and sodium dihydrogenphosphate (1.5g) at room
temperature, and the mixture was stirred for 3 hours. To
30 the mixture was added 1N hydrochloric acid, and the mixture
was extracted with ethyl acetate. The organic layer was
washed with sodium thiosulfate and saturated brine, and
dried with magnesium sulfate. Under reduced pressure, the
mixture was concentrated, and the precipitated crystals
35 were collected by filtration, which were washed with
diethylether to give colorless crystals of 2-(4-

methylphenyl)benzofuran-5-carboxylic acid (395mg).

m.p. 279-283 °C

¹H-NMR (200MHz, CDCl₃) δ 2.38 (3H, s), 7.34 (2H, d, J=8.2 Hz), 7.48 (1H, s), 7.70 (1H, d, J=8.8 Hz), 7.84 (2H, d, J=8.2 Hz), 7.92 (1H, dd, J=8.8, 1.2 Hz), 8.26 (1H, d, J=1.2 Hz).

IR (KBr) 2989, 1689, 1416, 1291, 768 cm⁻¹

Anal. Calcd. for C₁₆H₁₂O₃

Calcd. C, 76.18 ; H, 4.79.

Found. C, 76.11 ; H, 4.74.

10 Reference Example 205

To a solution of ethyl vanillate (2.50g) and triethylamine (3.6ml) in dichloromethane (50ml) was added at 0°C trifluoromethanesulfonic acid anhydride (2.6ml), and the mixture was stirred for 1.5 hours. To the mixture was added water (15ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:15) to give yellow oil of ethyl 3-methoxy-4-trifluoromethane-sulfonyloxybenzoate (3.96g).

¹H-NMR (200MHz, CDCl₃) δ 1.41 (3H, t, J=7.1 Hz), 3.99 (3H, s), 4.41 (2H, q, J=7.1 Hz), 7.28 (1H, d, J=7.6 Hz), 7.67-7.72 (2H, m).

25 IR (neat) 1726, 1606, 1502, 1466, 1427, 1292, 1246, 1207, 1142, 1109, 1030, 833, 768, 617 cm⁻¹

Reference Example 206

To a solution of ethyl 3-methoxy-4-trifluoromethane-sulfonyloxybenzoate (3.95g), 4-methylphenylacetylene (1.54g) and triethylamine (5.0ml) in DMF (40ml) was added bistrisphenylphosphine palladium dichloride (0.25g), and the mixture was stirred at 100°C for 3 hours and then cooled to room temperature. To the mixture was added water, and the mixture was extracted with diethylether. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was

concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:9) and recrystallized from ethyl acetate/hexane to give pale yellow crystals of ethyl 3-methoxy-4-[2-(4-methylphenyl)-ethynyl]-benzoate (2.02g).

m.p. 71-73 °C

¹H-NMR (200MHz, CDCl₃) δ 1.41 (3H, t, J=7.1 Hz), 2.37 (3H, s), 3.97 (3H, s), 4.39 (2H, q, J=7.1 Hz), 7.16 (2H, d, J=7.9 Hz), 7.47 (2H, d, J=7.9 Hz), 7.53 (1H, d, J=8.0 Hz), 7.57 (1H, d, J=1.6 Hz), 7.63 (1H, dd, J=8.0, 1.6 Hz).

IR (KBr) 1711, 1410, 1294, 1236, 1099, 1036, 812, 762 cm⁻¹

Anal. Calcd. for C₁₉H₁₈O₃,

Calcd. C, 77.53 ; H, 6.16.

Found. C, 77.48 ; H, 6.01.

15 Reference Example 207

A mixture of ethyl 3-methoxy-4-(4-methylphenyl)-ethynylbenzoate (1.5g) and pyridinium chloride (9.0g) was stirred at 200°C for 2 hours, and then cooled to 100°C. To the mixture was added DMF (20ml), and the mixture was cooled to room temperature. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the precipitated crystals were collected by filtration, which were washed with diethylether and hexane to give pale yellow crystals of 2-(4-methylphenyl)benzofuran-6-carboxylic acid (0.84g).

m.p. 270-272 °C

¹H-NMR (200MHz, DMSO-d₆) δ 2.38 (3H, s), 7.35 (2H, d, J=8.2 Hz), 7.47 (1H, s), 7.72 (1H, d, J=8.0 Hz), 7.85-7.89 (3H, m), 8.11 (1H, s).

IR (KBr) 2972, 1677, 1612, 1498, 1413, 1300, 1230, 798 cm⁻¹

Anal. Calcd. For C₁₆H₁₂O₃

Calcd. C, 76.18 ; H, 4.79.

Found. C, 76.05 ; H, 4.54.

Reference Example 208

To a solution of ethyl 7-(4-methylthiophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (198.5mg) in THF (20ml) was added at 0°C 70% 3-chloroperbenzoic acid (317mg), and the mixture was stirred at 0°C for 30 minutes and then at room temperature for 1 hour. To the mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes and then extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:1) to give colorless crystals of ethyl 7-(4-methylsulfonylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (221.8mg).
m.p. 150-153 °C
¹H-NMR (200MHz, CDCl₃) δ 1.37 (3H, t, J=7.2 Hz), 3.03 (2H, t, J=4.5 Hz), 3.10 (3H, s), 4.30 (2H, q, J=7.2 Hz), 4.33 (2H, t, J=4.5 Hz), 7.10 (1H, d, J=8.4 Hz), 7.50 (1H, dd, J=8.4, 2.2 Hz), 7.60 (1H, d, J=2.2 Hz), 7.65 (1H, s), 7.75 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz).
IR (KBr) 1693, 1595, 1485, 1302, 1252, 1230, 1213, 1146, 1092, 825 cm⁻¹
Anal. Calcd. for C₂₀H₂₀O₅S
Calcd. C, 64.50 ; H, 5.41 ; S, 8.61.
Found. C, 64.36 ; H, 5.40 ; S, 8.53.
Reference Example 209

To a solution of ethyl 7-(4-methylsulfonylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (180mg) in THF/ethanol (5/5ml) was added at room temperature 1N sodium hydroxide solution (1ml), and the mixture was stirred for 4 days. To the mixture was added 1N hydrochloric acid (10ml), and the mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate. Under reduced pressure, the mixture was concentrated. The resulting crystals were collected by filtration, which were washed with water, ethanol and diethylether to give

colorless crystals of 7-(4-methyl-sulfonylphenyl)-2,3-dihydrobenzoxepine-4-carboxylic acid (148.2mg).

m.p. 275 °C (dec.)

¹H-NMR (200MHz, DMSO-d₆) δ 2.84-2.94 (2H, m), 3.25 (3H, s),
5 4.23-4.34 (2H, m), 7.10 (1H, d, J=8.4 Hz), 7.64-7.75 (2H, m), 7.92-8.04 (5H, m).

IR (KBr) 3018, 1674, 1308, 1267, 1147, 829, 783, 760, 636, 546cm⁻¹

Anal. Calcd. for C₁₈H₁₆O₃S·0.2H₂O

10 Calcd. C, 62.13 ; H, 4.75 ; S, 9.21.

Found. C, 62.19 ; H, 4.69 ; S, 9.06.

Reference Example 210

A mixture of 4-bromothiophenol (24.8g), ethyl 4-bromo-butyrate (30.7g) and potassium carbonate (36.2g) in
15 DMF (100ml) was stirred at room temperature overnight. Under reduced pressure, the solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried with magnesium sulfate. Under
20 reduced pressure, the mixture was concentrated, and to the residue was added methanol (120ml) and 1N sodium hydroxide solution (240ml). The mixture was stirred at room temperature overnight, and to the mixture was added water. The mixture was washed with ethyl acetate, and to the aqueous
25 layer was added concentrated hydrochloric acid to make the solution acidic. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to colorless prism of 4-(4-bromophenylthio)butyric acid (31.8g).

¹H-NMR (200MHz, CDCl₃) δ 1.87-2.02 (2H, m), 2.53 (2H, t, J=7.1 Hz), 2.96 (2H, t, J=7.2 Hz), 7.21 (2H, d, J=8.8 Hz), 7.41 (2H, d, J=8.8 Hz).

IR (KBr) 1699 cm⁻¹

35 Anal. Calcd. for C₁₀H₁₁O₂BrS

Calcd. C, 43.65 ; H, 4.03.

Found. C, 43.70 ; H, 3.93.

Reference Example 211

A mixture of 4-(4-bromophenylthio)butyric acid (31.8g) and polyphosphoric acid (250g) was stirred at 100°C for 1 hour. The mixture was added to ice/water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown prism of 7-bromo-2,3,4,5-tetrahydro-1-benzo-thiepin-5-one (13.6g).

¹H-NMR (200MHz, CDCl₃) δ 2.22-2.35 (2H, m), 2.94-3.08 (4H, m), 7.33 (1H, d, J=8.0 Hz), 7.44 (1H, dd, J=8.0, 2.6 Hz), 7.96 (1H, d, J=2.6 Hz).

IR (KBr) 1682 cm⁻¹

Anal. Calcd. for C₁₀H₉OBrS
Calcd. C, 46.71 ; H, 3.53.
Found. C, 46.71 ; H, 3.45.

Reference Example 212

To a solution of 7-bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one (13.5g) in dimethyl carbonate (200ml) was added at room temperature sodium methoxide (14.2g), and the mixture was refluxed for 8 hours under nitrogen atmosphere. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown prism of methyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate (11.5g).

¹H-NMR (200MHz, CDCl₃) δ 2.40-2.84 (6H, m), 3.16-3.27 (2H, m), 3.75 (3H, s), 4.47-4.56 (1H, m), 7.33 (1H, d, J=8.4 Hz), 7.47 (1H, dd, J=8.4, 2.6 Hz), 7.99 (1H, d, J=2.6 Hz).

IR (KBr) 1750-cm⁻¹

Anal. Calcd. for C₁₂H₁₁O₃BrS
Calcd. C, 45.73 ; H, 3.52.
Found. C, 46.01 ; H, 3.48.

Reference Example 213

A solution of methyl 7-bromo-5-oxo-2,3,4,5-tetrahydro-1-benzothiepine-4-carboxylate (24.94g) in THF (200ml) was cooled to -20°C, and to the mixture was added dropwise a solution of sodium borohydride (2.99g) in methanol (30ml). While the temperature of the mixture was kept at -15 to 20°C, the mixture was stirred for 1 hour. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue (24.38g) was dissolved in THF (200ml). To the mixture was added triethylamine (26ml) and then to the mixture was added dropwise at 0°C methanesulfonyl chloride (9.2ml). The mixture was stirred at 0°C for 30 minutes and then at room temperature for 15 hours. To the mixture was added dropwise 1,8-diaza-bicyclo[5.4.0]-7-undecene (17.9g), and the mixture was stirred for 3 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:10). Under reduced pressure, the mixture was concentrated, and the resulting crystals were recrystallized from ethyl acetate/hexane to give pale yellow crystals of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (11.00g).

m.p. 94-95 °C

¹H-NMR (200MHz, CDCl₃) δ 2.94-3.00 (2H, m), 3.15-3.21 (2H, m), 3.83 (3H, s), 7.28-7.33 (2H, m), 7.51 (1H, d, J=1.2 Hz), 7.70 (1H, s).

Anal. Calcd. for C₁₂H₁₁O₂BrS

Calcd. C, 48.17 ; H, 3.71.

Found. C, 48.37 ; H, 3.77.

Reference Example 214

Under argon atmosphere, a mixture of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.5g), 4-methoxyphenyl borate (0.84g) and potassium carbonate (1.39g) in toluene/ethanol/water (50/5/5ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine) palladium (0.17g), and the mixture was refluxed for 24 hours and then cooled. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:15→1:9→1:4→1:2) to give pale yellow crystals of methyl 7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (1.40g).

m.p. 117-120 °C

¹H-NMR (200MHz, CDCl₃) δ 2.97-3.04 (2H, m), 3.19-3.25 (2H, m), 3.84 (3H, s), 3.86 (3H, s), 6.98 (2H, d, J=8.8 Hz), 7.39 (1H, dd, J=8.0, 2.2 Hz), 7.48-7.54 (3H, m), 7.57 (1H, d, J=2.2 Hz), 7.88 (1H, br s).

IR (KBr) 1716, 1630, 1606, 1520, 1479, 1431, 1281, 1250, 1221, 1186, 1020, 835, 814 cm⁻¹

Anal. Calcd. for C₁₉H₁₈O₃S

Calcd. C, 69.91 ; H, 5.56.

Found. C, 70.22 ; H, 5.65.

Reference Example 215

To a solution of methyl 7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (0.50g) in ethanol/THF (10/10ml) was added at room temperature 1N sodium hydroxide solution (2ml), and the mixture was stirred for 18 hours. To the mixture was added 1N hydrochloric acid (2ml). Under reduced pressure, the mixture was concentrated. To the mixture was added water, and the precipitates were collected by filtration, which were washed with 2-propanol, diethylether and hexane to give pale yellow solid of 7-(4-methoxyphenyl)-2,3-dihydro-1-benzo-thiepine-4-carboxylic acid (508mg). This compound

was used for the following reaction, without subjecting further purification.

¹H-NMR (200MHz, DMSO-d₆) δ 2.87 (2H, t, J=5.7 Hz), 3.11 (2H, t, J=5.7 Hz), 3.80 (3H, s), 7.01 (2H, d, J=8.8 Hz), 7.33-7.42 (2H, m), 7.50-7.55 (2H, m), 7.62 (2H, d, J=8.8 Hz).
IR (KBr) 3356, 1633, 1608, 1518, 1358, 1246, 1178, 1020, 825 cm⁻¹

Reference Example 216

Under argon atmosphere, a mixture of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.70g), 4-morpholinophenyl borate (581.3mg) and potassium carbonate (0.65g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine) palladium (0.14g), and the mixture was refluxed for 20 hours and then cooled. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/dichloromethane=1:4) to give yellow crystals of methyl 7-(4-morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (664.4mg).
m.p. 154-156 °C

¹H-NMR (200MHz, CDCl₃) δ 2.97-3.02 (2H, m), 3.20-3.25 (6H, m), 3.84 (3H, s), 3.87-3.91 (4H, m), 6.98 (2H, d, J=8.8 Hz), 7.35-7.43 (1H, m), 7.49-7.58 (4H, m), 7.88 (1H, s).
IR (KBr) 1709, 1606, 1520, 1448, 1274, 1242, 1232, 120, 926, 816 cm⁻¹

Anal. Calcd. for C₂₂H₂₃NO₃S

Calcd. C, 69.26 ; H, 6.08 ; N, 3.67.

Found. C, 69.43 ; H, 6.01 ; N, 3.81.

Reference Example 217

To a solution of methyl 7-(4-morpholinophenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (0.55g) in ethanol/THF (30/30ml) was added at room temperature 1N sodium hydroxide solution (1.8ml), and the mixture was

stirred for 6 days and then refluxed for 2 hours. To the mixture was added 1N hydrochloric acid (1.8ml). The resulting solid was collected by filtration, which was washed with ethanol and diethylether to give yellow powder of 7-(4-morpholinophenyl)-2,3-dihydro-1-benzo-thiepine-4-carboxylic acid (502.2mg).

m.p. 280 °C (dec.)

¹H-NMR (200MHz, DMSO-d₆) δ 2.88 (2H, t, J=5.3 Hz), 3.05-3.25 (6H, m), 3.67-3.82 (4H, m), 7.02 (2H, d, J=8.7 Hz), 7.43-7.54 (2H, m), 7.61 (2H, d, J=8.7 Hz), 7.75 (1H, s), 7.81 (1H, s).

IR (KBr) 2967, 1709, 1684, 1608, 1520, 1232, 1120, 926, 814 cm⁻¹

Anal. Calcd. for C₂₁H₂₁NO₃S

Calcd. C, 68.64 ; H, 5.76 ; N, 3.81.

Found. C, 68.68 ; H, 5.62 ; N, 3.69.

Reference Example 218

Under argon atmosphere, a mixture of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.5g), 3,4-methylenedioxyphenyl borate (0.92g) and potassium carbonate (1.39g) in toluene/ethanol/water (50/5/5ml) was stirred at room temperature 1 hours. To the mixture was added tetrakis(triphenylphosphine) palladium (0.29g), and the mixture was refluxed for 16 hours and cooled. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give pale yellow crystals of methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (1.55g).

m.p. 126-129 °C

¹H-NMR (200MHz, CDCl₃) δ 2.97-3.06 (2H, m), 3.19-3.24 (2H, m), 3.84 (3H, s), 6.01 (2H, s), 6.88 (1H, d, J=8.8 Hz), 7.02-7.08 (2H, m), 7.35 (1H, dd, J=8.0, 1.8 Hz), 7.50 (1H, d, J=8.4 Hz), 7.53 (1H, d, J=1.8 Hz), 7.87 (1H, br s).

IR (KBr) 1709, 1471, 1435, 1248, 1223, 1186, 1034, 928, 804 cm^{-1}

Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_4\text{S}$

Calcd. C, 67.04 ; H, 4.74.

5 Found. C, 67.19 ; H, 4.61.

Reference Example 219

To a solution of methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (0.6g) in ethanol/ THF (10/10ml) was added at
10 room temperature 1N sodium hydroxide solution (2ml), and the mixture was stirred for 64 hours. To the mixture was added 1N hydrochloric acid (3ml), and the mixture was concentrated. The resulting solid was collected by
15 filtration, which was washed with water, 2-propanol and diisopropylether to give pale yellow powder of 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (510.6mg).

m.p. 227-229 °C

^1H -NMR (200MHz, $\text{DMSO}-d_6$) δ 2.86-2.92 (2H, m), 3.14-3.20 (2H, m), 6.07 (2H, s), 6.99 (1H, d, $J=8.2$ Hz), 7.21 (1H, dd, $J=8.2$, 1.8 Hz), 7.33 (1H, d, $J=1.8$ Hz), 7.44-7.53 (2H, m), 7.77-7.82 (2H, m).

IR (KBr) 2895, 1672, 1473, 1288, 1252, 1225, 1039, 933, 806 cm^{-1}

25 Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{O}_4\text{S}$

Calcd. C, 66.24 ; H, 4.32.

Found. C, 66.01 ; H, 4.44.

Reference Example 220

To a suspension of 4-phenylpiperidine (5.0g) in
30 acetonitrile (100ml) was added triethylamine (8.64ml) and then was added dropwise at 0°C a solution of p-toluene-sulfonyl chloride (6.50g) in acetonitrile (30ml). The mixture was stirred at 0°C for 2 hours. Under reduced
35 pressure, the solvent was evaporated, and to the residue was water. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and

dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the resulting crystals were collected by filtration, which were washed with hexane to give colorless crystals of 1-(4-methylphenylsulfonyl)-

5 4-phenylpiperidine (8.93g).

m.p. 153-154 °C

¹H-NMR (200MHz, CDCl₃) δ 1.83-1.95 (4H, m), 2.26-2.43 (3H, m), 2.45 (3H, s), 3.87-3.99 (2H, m), 7.13-7.30 (5H, m), 7.35 (2H, d, J=8.0 Hz), 7.69 (2H, d, J=8.0 Hz).

10 IR (KBr) 1336, 1165, 1092, 933, 725, 700, 651, 577, 546 cm⁻¹

Anal. Calcd. for C₁₈H₂₁NO₂S

Calcd. C, 68.54 ; H, 6.71 ; N, 4.44.

Found. C, 68.31 ; H, 6.64 ; N, 4.40.

Reference Example 221

15 To a solution of 1-(4-methylphenylsulfonyl)-4-phenylpiperidine (1.0g) and 1,1-dichloromethylmethylether (0.57ml) in dichloromethane (5ml) was added at 0°C a solution of titanium tetrachloride (0.7ml) in dichloromethane (5ml), and the mixture was stirred at room temperature for 2 hours.

20 The mixture was added to stirred ice/water to stop the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution and saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was

25 concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:4→1:2) to give pale yellow crystals of 4-[1-(4-methylphenylsulfonyl)-piperidin-4-yl]benzaldehyde (0.381g). (469.4mg of the starting materials were collected)

30 m.p. 134-137 °C

¹H-NMR (200MHz, CDCl₃) δ 1.75-1.96 (4H, m), 2.29-2.58 (3H, m), 2.46 (3H, s), 3.90-4.03 (2H, m), 7.29-7.37 (4H, m), 7.69 (2H, d, J=8.4 Hz), 7.82 (2H, d, J=8.4 Hz), 9.97 (1H, s).

IR (KBr) 1697, 1603, 1333, 1159, 937, 721, 581, 546 cm⁻¹

35 Anal. Calcd. for C₁₉H₂₁NO₃S

Calcd. C, 66.45 ; H, 6.16 ; N, 4.08.

Found. C, 66.31 ; H, 6.08 ; N, 4.38.

Reference Example 222

To a suspension of (3-carboxypropyl)triphenylphosphonium bromide (16.5g) in THF (170ml) was added at room temperature potassium t-butoxide (8.63g), and the mixture was stirred at 60°C for 10 minutes and then cooled to room temperature. To the mixture was added a solution of 4-[1-(4-methylphenylsulfonyl)piperidin-4-yl]benzaldehyde (4.40g) in THF (20ml), and the mixture was stirred at 60°C for 1 hour. To the mixture was added water (80ml) and the mixture was extracted with toluene (80ml). To the aqueous layer was added 1N hydrochloric acid to make the solution pH 3, and the mixture was extracted with ethyl acetate. The organic layer was washed three times with 2% sodium bicarbonate solution, and then with 1N hydrochloric acid and saturated brine (X3). Under reduced pressure, the mixture was concentrated, and the residue was dissolved in THF (150ml). To the mixture was added Pd-C (0.5g), and the mixture was stirred under hydrogen atmosphere for 5 hours. By filtration Pd-C was removed, and the filtrate was concentrated under reduced pressure. The resulting crystals were collected by filtration, which were washed with hexane to give colorless crystals of 5-[4-[1-(4-methylphenylsulfonyl)piperidin-4-yl]phenyl]pentanoic acid (4.63g).
m.p. 164-170 °C
¹H-NMR (200MHz, CDCl₃) δ 1.58-1.70 (4H, m), 1.79-1.91 (4H, m), 2.25-2.42 (5H, m), 2.45 (3H, s), 2.54-2.65 (2H, m), 3.84-3.97 (2H, m), 7.04 (2H, d, J=8.2 Hz), 7.10 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.3 Hz), 7.68 (2H, d, J=8.3 Hz).
IR (KBr) 2937, 1703, 1335, 1163, 926, 725, 546 cm⁻¹
Anal. Calcd. for C₂₃H₂₉NO₄S
Calcd. C, 66.48 ; H, 7.03 ; N, 3.37.
Found. C, 66.66 ; H, 7.00 ; N, 3.50.

Reference Example 223

To a solution of 5-[4-[1-(4-methylphenylsulfonyl)-

- piperidin-4-yl]phenyl]pentanoic acid (0.50g) in THF (10ml) were added at room temperature oxalyl chloride (0.21ml) and a drop of DMF, and the mixture was stirred for 1 hour. Under reduced pressure, the mixture was concentrated, and the residue was dissolved in dichloromethane (10ml). To the mixture was added at 0°C aluminum chloride (0.35g), and the mixture was stirred at 0°C for 30 minutes and then at room temperature for 5 minutes. The mixture was added to ice/water, and the mixture was extracted with ethyl acetate.
- 10 The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give colorless crystals of 3-[1-(4-methylphenylsulfonyl)-piperidin-4-yl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (0.32g).
- 15 m.p. 165-169 °C
- ¹H-NMR (200MHz, CDCl₃) δ 1.74-1.93 (8H, m), 2.24-2.43 (3H, m), 2.46 (3H, s), 2.68-2.76 (2H, m), 2.85-2.95 (2H, m), 3.85-4.00 (2H, m), 7.14 (1H, d, J=8.0 Hz), 7.22 (1H, dd, J=8.0, 1.8 Hz), 7.35 (2H, d, J=8.2 Hz), 7.50 (1H, d, J=1.8 Hz), 7.68 (2H, d, J=8.2 Hz).
- IR (KBr) 1674, 1333, 1242, 1161, 1093, 933, 721, 546
- 25 cm⁻¹
- Anal. Calcd. for C₂₃H₂₇NO₃S
Calcd. C, 69.49 ; H, 6.85 ; N, 3.52.
Found. C, 69.10 ; H, 6.62 ; N, 3.71.
Reference Example 224
- 30 To a solution of 3-[1-(4-methylphenylsulfonyl)-piperidin-4-yl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (3.25g) in dimethyl carbonate (50ml) was added at room temperature sodium methoxide (2.21g), and the mixture was refluxed for 4.5 hours and cooled to room temperature. To the mixture was added 1N hydrochloric acid (100ml), and the mixture was extracted with ethyl acetate. The organic layer
- 35

was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated to give crude product (3.91g). The resulting crude product was dissolved in THF (150ml), and to the mixture was added at -40°C a solution of sodium boro hydride (0.31g) in methanol (10ml). The mixture was stirred at -10 to -20°C for 1 hour. To the mixture was added a solution of sodium boro hydride (0.31g) in methanol (10ml), and the mixture was stirred for 1.5 hours. To the mixture was added acetone (2ml), and the mixture was stirred for 30 minutes. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was dissolved in THF (40ml). To the mixture was added triethylamine (3.42ml). To the mixture was added at 0°C methanesulfonyl chloride (0.95ml), and the mixture was stirred at 0°C for 30 minutes and then at room temperature for 30 minutes. To the mixture was added 1,8-diaza-bicyclo[5,4,0]-7-undecene (3.7ml), and the mixture was stirred for 14 hours. To the mixture was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give colorless crystals of methyl 4-[1-(4-methylphenyl-sulfonyl)piperidin-4-yl]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (2.01g).

m.p. 169-173 °C

¹H-NMR (200MHz, CDCl₃) δ 1.75-1.92 (2H, m), 1.95-2.09 (2H, m), 2.26-2.43 (3H, m), 2.45 (3H, s), 2.62 (2H, t, J=6.2 Hz), 2.75-2.80 (2H, m), 3.81 (3H, s), 3.87-3.98 (2H, m), 6.98-7.10 (3H, m), 7.35 (2H, d, J=8.6 Hz), 7.65 (1H, s), 7.68 (2H, d, J=8.6 Hz).

IR (KBr) 1709, 1433, 1336, 1234, 1198, 1161, 1092, 933, 721,

548 cm^{-1}

Anal. Calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_4\text{S}$

Calcd. C, 68.31 ; H, 6.65 ; N, 3.19. .

Found. C, 68.23 ; H, 6.60 ; N, 3.04.

5 Reference Example 225

To a solution of methyl 4-[1-(4-methylphenylsulfonyl)piperidin-4-yl]-6,7-dihydro-5H-benzocycloheptene-8-carboxylate (1.0g) in ethanol/THF (20/40ml) was added at room temperature 1N sodium hydroxide solution (2.7ml), and the mixture was stirred for 13 hours. Under reduced pressure, the mixture was concentrated. To the mixture was added water, and the mixture was washed with ethyl acetate. To the aqueous layer was added 1N hydrochloric acid (5ml), and the mixture was extracted with ethyl acetate/THF. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the mixture was concentrated, and the resulting colorless crystals were collected by filtration, which were washed with hexane to give colorless crystals of 4-[1-(4-methylphenylsulfonyl)piperidin-4-yl]-6,7-dihydro-5H-benzocycloheptene-8-carboxylic acid (565.4mg). m.p. 255-257 °C

^1H -NMR (200MHz, CDCl_3) δ 1.74-1.94 (4H, m), 1.96-2.11 (2H, m), 2.28-2.48 (3H, m), 2.46 (3H, s), 2.65 (2H, t, $J=6.6$ Hz), 2.78-2.84 (2H, m), 3.87-4.01 (2H, m), 7.00-7.12 (3H, m), 7.35 (2H, d, $J=8.2$ Hz), 7.72 (2H, d, $J=8.2$ Hz), 7.77 (1H, s).

IR (KBr) 3008, 1674, 1352, 1294, 1273, 1255, 1163, 931, 721, 548 cm^{-1}

30 Anal. Calcd. for $\text{C}_{24}\text{H}_{27}\text{NO}_4\text{S}$

Calcd. C, 67.74 ; H, 6.40 ; N, 3.29.

Found. C, 67.97 ; H, 6.69 ; N, 3.11.

Reference Example 226

In THF (126ml) was dissolved 5-bromo-2-methylthiophene (10.5g), and to the mixture was added dropwise at -78°C 1.6N n-butyl lithium/hexane (40.8ml). The mixture

was stirred for 1 hour, and to the mixture was added dropwise a solution of trimethyl borate (18.5g) in THF (40ml). The mixture was stirred for 15 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (63ml), and the mixture was stirred for 15 minutes. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was washed with isopropylether to give 5-methyl-2-thienyl borate (4.6g).
¹H-NMR (200MHz, CDCl₃) δ 2.59 (3H, s), 6.93 (1H, d, J=3.4Hz), 7.79 (1H, d, J=3.4Hz)

Reference Example 227

In toluene/ethanol/water (10/1/1) (24ml) was dissolved methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (560mg), and to the mixture were added 5-methyl-2-thienyl borate (875mg) and potassium carbonate (1.56g). The mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphine palladium (260mg), and the mixture was stirred at 100°C for 24 hours and cooled to room temperature. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (hexane/acetone=12/1) to give methyl 7-(5-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (345mg).

¹H-NMR (200MHz, CDCl₃) δ 2.28 (3H, s), 2.99 (2H, t, J=4.8Hz), 3.83 (3H, s), 4.28 (2H, t, J=4.8Hz), 6.82 (1H, d, J=1.2Hz), 7.05 (1H, d, J=8.4Hz), 7.45 (1H, dd, J=8.4, 2.4), 7.54 (1H, d, J=2.4Hz), 7.61 (1H, s)

Reference Example 228

In THF (10.5ml) and methanol (5.2ml) was dissolved methyl 7-(5-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (525mg), and to the mixture was added 1N sodium

hydroxide (10.5ml). The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the organic solvent was removed, and to the residue was added ethyl acetate. The mixture was extracted with water, and to the aqueous layer was added 6N hydrochloric acid to make the solution pH 4-5, which was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed to give 7-(5-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (410mg).

¹H-NMR (200MHz, DMSO-d₆) δ 2.23 (3H, s), 2.87 (2H, t, J=4.4Hz), 4.24 (2H, t, J=4.4Hz), 6.99 (1H, d, J=8.4Hz), 7.07 (1H, s), 7.31 (1H, d, J=1.4Hz), 7.49 (1H, dd, J=8.4, 2.2Hz), 7.58 (1H, s), 7.74 (1H, d, J=2.2Hz).

Reference Example 229

In toluene/ethanol/water (10/1/1) (12ml) was dissolved methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (700mg), and to the mixture were added 3-thienyl borate (422mg) and potassium carbonate (0.98g). The mixture was stirred at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (136mg). The mixture was stirred at 100°C for 13 hours and cooled to room temperature, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (hexane/acetone=3/1) to give methyl 7-(3-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (610mg).

¹H-NMR (200MHz, CDCl₃) δ 3.00 (2H, t, J=4.2Hz), 3.83 (3H, s), 4.30 (2H, t, J=4.2Hz), 7.01 (1H, d, J=8.4Hz), 7.33-7.40 (3H, m), 7.49 (1H, dd, J=8.4, 2.4), 7.66 (1H, d, J=2.4Hz), 7.64 (1H, s).

Reference Example 230

In THF (24ml) and methanol (6ml) was dissolved methyl 7-(3-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate

(610mg), and to the mixture was added 1N sodium hydroxide (12ml). The mixture was stirred at room temperature for 3 hours. Under reduced pressure, the organic solvent was removed, and to the residue was added ethyl acetate. The mixture was extracted with water, and to the aqueous layer was added 6N hydrochloric acid to make the solution pH 4-5, which was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed to give 7-(3-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (500mg).

¹H-NMR (200MHz, DMSO-d₆) δ 2.87 (2H, t, J=4.6Hz), 4.24 (2H, t, J=4.6Hz), 7.00 (1H, d, J=8.4Hz), 7.60-7.85 (4H, m), 7.84-7.89 (2H, m)

Reference Example 231

In ether (160ml) was dissolved 3-methylthiophene (20g), and to the mixture was added N,N,N,N-tetramethylethylenediamine (26g). To the mixture was added dropwise at room temperature 1.6N n-butyl lithium/hexane (140ml), and the mixture was refluxed for 30 minutes. The mixture was cooled to -70°C, and to the mixture was added dropwise a solution of trimethyl borate (63.5g) in THF (64ml). The mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (285ml), and the mixture was stirred for 15 minutes. The mixture was washed with water and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was washed with isopropylether to give 4-methyl-2-thienyl borate (6.0g).

¹H-NMR(200MHz,CDCl₃) δ 2.36 (3H, s), 7.35 (1H), 7.78 (1H, s)

Reference Example 232

In toluene/ethanol/water (10/1/1) (8.4ml) was dissolved methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg), and to the mixture were added 4-methyl-2-thienyl borate (334mg) and potassium carbonate (651g). The mixture was stirred at room temperature for 30

minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (97mg). The mixture was stirred at 100°C for 24 hours and cooled to room temperature. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the resulting residue was purified with silica gel column chromatography (hexane/acetone=8/1) to give methyl 7-(4-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (432mg).

¹H-NMR (200MHz, CDCl₃) δ 2.28 (3H, s), 2.99 (2H, t, J=4.8Hz), 3.83 (3H, s), 4.28 (2H, t, J=4.8Hz), 6.82 (1H, d, J=1.2Hz), 7.05 (1H, d, J=8.4Hz), 7.45 (1H, dd, J=8.4, 2.4Hz), 7.54 (1H, d, J=2.4Hz), 7.61 (1H, s)

Reference Example 233

In THF (10ml) was dissolved methyl 7-(4-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (420mg), and to the mixture was added 1N sodium hydroxide (8.4ml). The mixture was stirred at room temperature for 15 hours. Under reduced pressure, the organic solvent was removed, and to the residue was added ethyl acetate. The mixture was extracted with water, and to the aqueous layer was added 6N hydrochloric acid to make the solution pH 4-5, which was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed to give 7-(4-methyl-2-thienyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (320mg).

¹H-NMR (200MHz, DMSO-d₆) δ 2.23 (3H, s), 2.87 (2H, t, J=4.4Hz), 4.24 (2H, t, J=4.4Hz), 6.99 (1H, d, J=8.4Hz), 7.07 (1H, s), 7.31 (1H, d, J=1.4Hz), 7.49 (1H, dd, J=8.4, 2.2Hz), 7.58 (1H, s), 7.74 (1H, d, J=2.2Hz)

Reference Example 234

To methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (500mg) were added 4-fluorophenyl borate (272mg), potassium carbonate (537mg), water (1.5ml),

ethanol (1.5ml) and toluene (15ml). Under argon atmosphere, the mixture was stirred at room temperature for 1 hour, and to the mixture was added tetrakis(triphenylphosphine)palladium (61mg, 3mol%). Under argon atmosphere, the mixture was refluxed for 21 hours, and to the mixture was added ethyl acetate (100ml). The mixture was washed with water (50ml) and saturated brine (50ml), and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography to give methyl 7-(4-fluorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (310mg, 59%) as pale yellow crystals.

¹H NMR (200MHz, CDCl₃) δ 3.01 (2H, t, J=4.1Hz), 3.83 (3H, s), 4.31 (2H, t, J=4.8Hz), 7.03-7.17 (3H, m), 7.40-7.54 (4H, m), 7.66 (1H, s).

Reference Example 235

To methyl 7-(4-fluorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (0.27g) were added THF (5.0ml), ethanol (10.0ml) and 2N sodium hydroxide solution (1.0ml), and the mixture was stirred at room temperature for 19 hours.

Under reduced pressure, the solvent was removed, and the residue was diluted with water (100ml). The aqueous layer was made acidic with hydrochloric acid, and the mixture was extracted with ethyl acetate (100ml). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was crystallized and washed with hexane to give 7-(4-fluorophenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.22g, 86%) as white crystals.

¹H NMR (200MHz, CDCl₃) δ 3.03 (2H, t, J=4.8Hz), 4.33 (2H, t, J=4.6Hz), 7.05-7.17 (3H, m), 7.43-7.55 (4H, m), 7.76 (1H, s).

Reference Example 236

To 4-bromophenoxybutyric acid (75.0g) was added polyphosphoric acid (873g), and the mixture was stirred at 100°C for 45 minutes. The mixture was poured into ice (about

1.5kg), and the mixture was extracted with ethyl acetate (1.5L and 0.5L). The organic layer was washed with water (400ml×3), 1N sodium hydroxide solution (400ml×2), saturated sodium hydrogen carbonate solution (400ml×2),
5 water (400ml×3) and saturated brine (400ml×3), and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 7-bromo-2,3,4,5-tetrahydro-1-benzoxepin-5-one (38.6g, 55%, 132.5°C /0.33mmHg) as pale yellow oil.

10 Reference Example 237

To a solution of 5-bromo-2-fluorobenzaldehyde (0.49 g, 2.62 mmol) and ethyl 3-mercaptopropionate (0.37 ml, 2.88 mmol) in N,N-dimethylformamide (10 ml) was added potassium carbonate (0.90 g, 6.55 mmol), and the mixture was stirred
15 at room temperature for 1 hour and then at 70°C for 15 hours. The mixture was poured into ice-water, and made pH 4 with 1N hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with magnesium sulfate. The
20 solvent was evaporated, and the residue was purified with silica gel column chromatography [hexane:ethyl acetate (5:1)] to give ethyl 6-bromo-2H-thiochromene-3-carboxylate (0.45 g, 58%) as yellow powder, a part of which was recrystallized from ethanol to give pale yellow needles.
25 m.p. 87°C

¹H-NMR (CDCl₃) δ: 7.47 (1H, br s), 7.26-7.38 (2H, m), 7.14 (1H, d, J=8.0), 4.31 (2H, q, J=7.4), 3.73 (2H, d, J=1.2), 1.36 (3H, d, J=7.4).

Anal. Calcd for C₁₂H₁₁BrO₂S: C; 48.17, H; 3.71.

30 Found: C; 48.07, H; 3.77.

Reference Example 238

A solution of ethyl 6-bromo-2H-thiochromene-3-carboxylate (1.00 g, 3.34 mmol), 4-methylphenyl borate (0.55 g, 4.01 mmol) and tetrakis(triphenylphosphine)
35 palladium (0.19 g, 0.167 mmol) in 2M sodium carbonate (3.5 ml), ethanol (3 ml) and toluene (25 ml) was stirred at 80°C

for 24 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid and saturated brine, and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [hexane:ethyl acetate (5:1)] to give ethyl 6-(4-methylphenyl)-2H-thiochromene-3-carboxylate (1.02 g, 99%) as yellow powder.

m.p. 87°C

¹H-NMR (CDCl₃) δ: 7.62 (1H, br s), 7.40-7.46 (4H, m), 7.22-7.31 (3H, m), 4.31 (2H, q, J=7.0), 3.77 (2H, d, J=1.0), 2.40 (3H, s), 1.37 (3H, t, J=7.0).

Anal. Calcd for C₁₉H₁₈O₂S: C; 73.52, H; 5.84.

Found: C; 73.51, H; 5.65.

Reference Example 239

To a solution of ethyl 6-(4-methylphenyl)-2H-thiochromene-3-carboxylate (2.12 g, 6.84 mmol) in tetrahydrofuran (20 ml) and acetonitrile (20 ml) was added dropwise 1N sodium hydroxide (7 ml), and the mixture was stirred at 60°C for 2.5 hours. The solvent was evaporated, and the residue was dissolved in diethylether. The mixture was extracted with water. The organic layer was extracted with 0.5N sodium hydroxide, and both of the aqueous layers were made pH 3 with 6N hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated to give 6-(4-methyl-phenyl)-2H-thiochromene-3-carboxylic acid (1.83 g, 95%) as yellow powder.

m.p. 244°C

¹H-NMR (DMSO-d₆) δ: 7.44 (1H, d, J=1.8), 7.21-7.32 (4H, m), 7.05 (1H, d, J=8.4), 6.95 (2H, d, J=8.2), 3.41 (2H, d, J=1.0), 2.02 (3H, s).

Anal. Calcd for C₁₇H₁₄O₂S · 0.25H₂O: C; 71.18, H; 5.09.

Found: C; 70.90, H; 4.80.

Reference Example 240

To a solution of 4-nitrobenzaldehyde (6.0 g, 37.7 mmol) and ethyl β -aminopropionate hydrochloride (6.1 g, 37.7 mmol) in 1,2-dichloroethane (120 ml) was added triethylamine (5.3 ml, 37.7 mmol) and at 0°C was added little
5 by little triacetoxo boro hydride (11.8 g, 52.8 mmol). The mixture was stirred at room temperature for 1 hour, and to the mixture was added 37% formalin (4.0 ml, 49.0 mmol) and then at 0°C triacetoxo boro hydride (11.8 g, 52.8 mmol). The mixture was stirred at room temperature for 14 hours, and
10 the mixture was neutralized with saturated sodium hydrogen carbonate and extracted with dichloromethane. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated to give crude product, which was purified with silica gel column chromatography
15 [hexane:ethyl acetate (3:2)] to give ethyl 3-(N-methyl-N-(4-nitrobenzyl))aminopropionate (9.34 g, 93%) as pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.17 (2H, dd, $J=8.8, 1.8$), 7.49 (2H, d, $J=8.8$), 4.15 (2H, q, $J=7.4$), 3.61 (2H, s), 2.76 (2H, t, $J=7.2$), 2.52 (2H, t, $J=7.2$), 2.22 (3H, s), 1.26 (3H, t, $J=7.4$).

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$: C; 58.63, H; 6.81, N; 10.52.

Found: C; 58.24, H; 6.78, N; 10.23.

Reference Example 241

25 To a solution of 4-nitrobenzaldehyde (2.0 g, 13.2 mmol) and 2-methoxyethylamine (1.15 ml, 13.2 mmol) in 1,2-dichloroethane (40 ml) was added triethylamine (1.9 ml), and at 0°C was added little by little triacetoxo boro hydride (4.1 g). The mixture was stirred at room temperature for
30 1 hour was stirred, and to the mixture was added 37% formalin (1.4 ml) and then at 0°C triacetoxo boro hydride (4.1 g). The mixture was stirred at room temperature for 14 hours, neutralized with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The extract
35 was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated to give crude product

which was purified with silica gel column chromatography [hexane:ethyl acetate (1: 2)] to give 4-((N-(2-methoxy-ethyl)-N-methyl)aminomethyl)nitrobenzene (2.75 g, 93%) as pale yellow oil.

- 5 ¹H-NMR (CDCl₃) δ: 8.18 (2H, d, J=8.8), 7.53 (2H, d, J=8.8), 3.66 (2H, s), 3.53 (2H, t, J=5.6), 3.35 (3H, s), 2.63 (2H, t, J=5.6), 2.28 (3H, s).

Anal. Calcd for C₁₄H₂₀N₂O₃: C; 63.62, H; 7.63, N; 10.60.

Found: C; 63.54, H; 7.59, N; 10.51.

10 Reference Example 242

- To a solution of 4-nitrobenzaldehyde (1.76 g, 11.7 mmol) and 4-aminocyclohexanol (1.34 g, 13.2 mmol) in 1,2-dichloroethane (30 ml) was added triethylamine (1.6 ml) and at 0°C was added little by little triacetoxy boro hydride (3.7 g). The mixture was stirred at room temperature for 1 hour, and to the mixture was added 37% formalin (1.2ml) and then at 0°C triacetoxy boro hydride (3.7 g). The mixture was stirred at room temperature for 14 hours, neutralized with saturated sodium hydrogen carbonate and extracted with dichloromethane. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated to give crude product, which was purified with silica gel column chromatography [ethyl acetate:ethanol (2:1)] to give (E)-4-((N-(4-hydroxy-cyclohexyl)-N-methyl)aminomethyl)nitrobenzene (2.08 g, 67%) as pale yellow crystals, a part of which was recrystallized from ether/hexane to give pale yellow needles.

m.p. 87°C

- 30 ¹H-NMR (CDCl₃) δ: 8.17 (2H, d, J=8.6), 7.51 (2H, d, J=8.6), 3.51-3.65 (1H, m), 2.39-2.56 (1H, m), 2.18 (3H, s), 1.83-2.12 (4H, m), 1.20-1.51 (4H, m).

Anal. Calcd for C₁₄H₂₀N₂O₃: C; 63.62, H; 7.63, N; 10.68.

Found: C; 63.54, H; 7.59, N; 10.51.

Reference Example 243

- 35 To a solution of (E)-4-((N-(4-hydroxycyclohexyl)-N-methyl)aminomethyl)nitrobenzene (1.07 g, 4.05 mmol) in

ethyl acetate (30 ml) was added 5%-Pd/C (0.43 g), and the mixture was stirred under hydrogen atmosphere for 3.5 hours.

The mixture was filtered with sellaitite, and the filtrate was concentrated. The resulting residue was purified with silica gel column chromatography [ethyl acetate:methanol:triethylamine (9:1: 0.02) to give (E)-4-((N-(4-hydroxycyclohexyl)-N-methyl)aminomethyl)aniline (0.27 g, 28%) as yellow powder.
m.p. 105°C.

¹H-NMR (CDCl₃) δ: 7.09 (2H, d, J=8.6), 6.65 (2H, d, J=8.6), 3.46-3.70 (1H, m), 3.45 (2H, s), 2.35-2.53 (1H, m), 2.16 (3H, s), 1.84-2.10 (4H, m), 1.19-1.51 (4H, m).

Reference Example 244

To a solution of ethyl 3-(N-methyl-N-(4-nitrobenzyl))aminopropionate (1.51g, 5.68mmol) in acetic acid (30ml) was added iron (1.27g, 22.7mmol), and the mixture was stirred for 14 hours. The solvent was evaporated, and the precipitates were filtered with sellaitite and washed with ethyl acetate. The filtrate was diluted with water, made basic with potassium carbonate and extracted with ethyl acetate. The extracted was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:ethanol (2:1)] to give ethyl 3-(N-methyl-N-(4-aminobenzyl))aminopropionate (0.70g, 52%) as brown oil.

¹H-NMR (CDCl₃) δ: 7.07 (2H, d, J=8.6), 6.64 (2H, d, J=8.6), 4.13 (2H, q, J=6.8), 3.41 (2H, s), 3.30-3.60 (2H, m), 2.73 (2H, t, J=7.4), 2.51 (2H, t, J=7.4), 2.19 (3H, s), 1.25 (3H, t, J=6.8).

Reference Example 245

To a solution of 4-((N-(2-methoxyethyl)-N-methyl)aminomethyl)nitrobenzene (1.1 g, 4.91 mmol) in acetic acid (20 ml) was added iron (1.1 g, 19.6 mmol), and the mixture was stirred for 15 hours. The solvent was evaporated, and the precipitates were filtered with sellaitite and washed with

ethyl acetate. The filtrate was diluted with water, made basic with potassium carbonate and extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:methanol: triethylamine (7:1:0.02)] to give 4-((N-(2-methoxyethyl)-N-methyl)-aminomethyl)aniline (880 mg, 92%) as brown oil.

¹H-NMR (CDCl₃) δ: 7.09 (2H, d, J=8.4), 6.64 (2H, d, J=8.4), 3.50 (2H, t, J=5.8), 3.45 (2H, s), 3.33 (3H, s), 2.57 (2H, t, J=5.8), 2.24 (3H, s).

Reference Example 246

To a solution of 4-nitrobenzaldehyde (6.04 g, 40.0 mmol), N-methylethanolamine (3.00 g, 40.0 mmol) and triethylamine (5.6 ml, 40.0 mmol) in tetrahydrofuran (200 ml) was added triacetoxy boro hydride (26.8 g, 120 mmol), and the mixture was stirred for 21 hours. The mixture was diluted with ethyl acetate, and washed with saturated sodium hydrogen carbonate and saturated brine. The extract was dried, and the solvent was evaporated to give crude product, which was purified with silica gel column chromatography [ethyl acetate:ethanol (4:1)] to give 4-((N-(2-hydroxyethyl)-N-methyl)aminomethyl)nitrobenzene (7.08 g, 84%) as yellow oil.

¹H-NMR (CDCl₃) δ: 8.20 (2H, d, J=8.8), 7.50 (2H, d, J=8.8), 3.68 (2H, s), 3.68 (2H, t, J=5.6), 2.64 (2H, t, J=5.6), 2.52-2.70 (1H, m), 2.26 (3H, s).

Reference Example 247

To a solution of 4-((N-(2-hydroxyethyl)-N-methyl)aminomethyl)nitrobenzene (2.95 g, 14.1 mmol) in acetic acid (60 ml) was added iron (3.14 g, 56.2 mmol), and the mixture was stirred for 23 hours. The solvent was evaporated, and the precipitates were filtered with sellait and washed with ethyl acetate. The filtrate was diluted with water, made pH 10 with potassium carbonate and extracted with ethyl acetate. The extract was washed with

saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography [ethyl acetate:methanol:triethylamine (5:1:0.3)] to give 4-((N-(2-hydroxyethyl)-N-methyl)aminomethyl)aniline (1.25 g, 49%) as brown oil.
5 ¹H-NMR (CDCl₃) δ: 7.07 (2H, d, J=8.4), 6.65 (2H, d, J=8.4), 3.61 (2H, t, J=5.2), 3.46 (2H, s), 2.57 (2H, t, J=5.2), 2.20 (3H, s).

Reference Example 248

10 To THF(60ml) was added at -70°C n-butyllithium (1.59M hexane solution, 63ml, 100mmol). To the mixture was added dropwise (taking about 1 hour) a solution of 2,6-dibromopyridine (23.69g, 100mmol) in THF (140ml) at -60°C, and the mixture was stirred at -70°C for 15 minutes. To the mixture
15 was added DMF (12ml), and the mixture was stirred at the same temperature for 15 minutes. To the mixture was added 20% ammonium chloride solution (100ml), and the organic layer was separated. The aqueous layer extracted with ethyl acetate (100ml), and the organic layer was mixed with the
20 previous organic layer. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 150g, ethyl acetate/hexane=1/20), and the desired fraction was concentrated under
25 reduced pressure. To the residue was added diisopropylether (15ml), and insoluble materials were filtered, which were washed with diisopropylether (5ml×3) and dried under reduced pressure to give 6-bromo-2-pyridinecarbaldehyde (2.05g, 11.0mmol, 11%).
30 IR (KBr): 1732 cm⁻¹.
¹H-NMR (CDCl₃) δ: 7.65-8.00 (3H, m), 10.01 (1H, s).

Reference Example 249

In THF (10ml) was suspended sodium hydride (60%, 440mg, 11.0mmol), and to the mixture was added at -30°C a solution
35 of diethylphosphonoethyl acetate (2.47g, 11.0mmol) in THF (10ml). The mixture was stirred at the same temperature for

30 minutes, and to the mixture was added at -30°C a solution of 6-bromo-2-pyridinecarbaldehyde (1.86g, 10.0mmol) in THF (10ml). While warming the temperature of the mixture from -30°C to -10°C , the mixture was stirred for 1.5 hours. To the mixture was added diethylether (40ml), and the mixture was washed with water (20ml, 5ml \times 2) and saturated brine (5ml). The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added hexane (10ml), and the mixture was cooled to 0°C . The precipitated insoluble materials were filtered, which were washed with hexane cooled to 0°C , and dried under reduced pressure to give ethyl 6-bromo-2-pyridine-acrylate (2.00g, 7.81mmol, 78%).

IR (KBr): 1717, 1703 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) δ : 1.34 (3H, t, $J=7.1\text{Hz}$), 4.28 (2H, q, $J=7.1\text{Hz}$), 6.96 (1H, d, 15.8Hz), 7.30-7.65 (4H, m).

Reference Example 250

In 1,2-dimethoxyethane (4ml) were dissolved ethyl 6-bromo-2-pyridineacrylate (512mg, 2.00mmol) and 4-methylphenyl borate (299mg, 2.20mmol), and to the mixture were added sodium carbonate (424mg, 4.00 mmol), water (2ml) and tetrakis-(triphenylphosphine)palladium (116mg, 0.10mmol). The mixture was stirred at 80°C for 10 hours. To complete the reaction, 4-tolyl borate (150mg, 1.10mmol) and tetrakis(triphenyl-phosphine)palladium (116mg, 0.10mmol) were added at 80°C to the mixture, and the mixture was stirred for 14 hours. To the mixture was added ethyl acetate (30ml), and the mixture was water (5ml \times 2) and saturated brine (5ml). The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 15g, ethyl acetate/hexane=1/19), and the desired fraction was concentrated under reduced pressure to give ethyl 6-(4-methylphenyl)-2-pyridineacrylate (495mg, 1.85mmol, 93%).

IR (KBr): 1713 cm^{-1} .

¹H-NMR (CDCl₃) δ: 1.36 (3H, t, J=7.1Hz), 2.42 (3H, s), 4.30 (2H, q, J=7.1Hz), 7.10 (1H, d, 15.6Hz), 7.25-7.35 (3H, m), 7.65-7.85 (3H, m), 7.99 (2H, d, J=8.2Hz).

Reference Example 251

5 In methanol (5ml) was suspended ethyl 6-(4-methylphenyl)-2-pyridineacrylate (465mg, 1.74mmol), and to the mixture was added at 0°C 1N sodium hydroxide solution (5.22ml). The mixture was stirred at room temperature for 20 hours. To the mixture was added at 0°C 1N hydrochloric acid (5.22ml), and methanol was evaporated under reduced pressure. The aqueous layer extracted with ethyl acetate (30ml, 20ml). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. To the residue was added diisopropylether(5ml), and Insoluble materials were filtered, which were washed with diisopropylether and dried under reduced pressure to give 6-(4-methylphenyl)-2-pyridineacrylic acid (344mg, 1.44mmol, 83%).

¹H-NMR (CDCl₃) δ: 2.43 (3H, s), 7.15 (1H, d, 15.5Hz), 7.25-7.40 (1H, m), 7.31 (2H, d, J=8.5Hz), 7.70-7.85 (2H, m), 7.84 (1H, d, J=15.5Hz), 8.00 (2H, d, J=8.5Hz).

Reference Example 252

In 1,2-dimethoxyethane(12ml) were dissolved methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (566mg, 2.00mmol) and 3,4-methylenedioxyphenyl borate (465mg, 2.80mmol). To the mixture were added sodium carbonate (424mg, 4.00mmol), water (2ml) and tetrakis(triphenylphosphine)palladium (162mg, 0.14mmol), and the mixture was stirred at 80°C for 14 hours. To the mixture was added ethyl acetate (30ml), and the mixture was extracted with water (5ml×2) and saturated brine (5ml). The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 15g, ethyl acetate/hexane=1/19), and the desired fraction was concentrated under reduced pressure. To the residue was added

diisopropylether, and the insoluble materials were filtered, which were washed with diisopropylether and dried under reduced pressure to give methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate

5 (434mg, 1.34mmol, 67%).

IR (KBr): 1705 cm⁻¹.

¹H-NMR (CDCl₃) δ: 2.95-3.10 (2H, m), 3.83 (3H, s), 4.25-4.35 (2H, m), 6.01 (2H, s), 6.87 (1H, d, J=8.6Hz), 6.95-7.10 (3H, m), 7.40 (1H, dd, J=8.4, 2.4Hz), 7.47 (1H, d, J=2.2Hz), 7.65

10 (1H, s).

Reference Example 253

In methanol (5ml) was suspended 7-(3,4-methylenedioxy-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (399mg, 1.23mmol), and to the mixture was added 15 1N sodium hydroxide solution (3.69ml). The mixture was stirred at room temperature for 20 hours, and to the mixture was added 1N hydrochloric acid (3.69ml). The mixture was concentrated under reduced pressure, and to the residue was added water. Insoluble materials were filtered, which were

20 washed with water and diethylether and dried under reduced pressure to give 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid(321mg, 1.03mmol, 84%).

¹H-NMR (DMSO-d₆) δ: 2.80-2.95 (2H, m), 4.15-4.35 (2H, m), 25 6.05 (2H, s), 6.97 (1H, d, J=8.1Hz), 7.01 (1H, d, J=8.4Hz), 7.16 (1H, dd, J=8.1, 1.7Hz), 7.29 (1H, d, J=1.7Hz), 7.53 (1H, dd, J=8.4, 2.3Hz), 7.63 (1H, s), 7.74 (1H, d, J=2.3Hz).

Reference Example 254

In THF (100ml) was dissolved 1,2-methylenedioxy-4-bromobenzene (24.00g, 119mmol), and to the mixture was added dropwise at -55°C or less n-butyllithium (1.6M hexane solution, 82ml, 131mmol). The mixture was stirred at -70°C for 30 minutes, and the resulting mixture was added dropwise at -60°C or less to a solution of trimethyl borate 30 (18.61g, 179mmol) in tetrahydrofuran (50ml) with using cannula. The mixture was stirred at -70°C for 1 hour and

then for 2 hours with warming to room temperature. To the mixture were added 1N hydrochloric acid (130ml) and diethylether (150ml), and the organic layer was separated. The organic layer was washed with water (50×2ml) and saturated brine (50ml), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added diisopropylether (40ml), and insoluble materials were filtered, which were washed with diisopropylether (30ml×4) and dried under reduced pressure to give 3,4-methylenedioxyphenyl borate (6.79g, 40.9mmol, 34%).

¹H-NMR (DMSO-d₆) δ: 5.99 (2H, s), 6.8-6.95 (1H, m), 7.25-7.45 (2H, m).

Reference Example 255

In methanol (250ml) was suspended 5-nitrosalicylic acid (50.0g, 273mmol), and to the mixture was added sulfuric acid (6ml). The mixture was stirred at 100°C for 24 hours and the cooled to room temperature. The precipitated insoluble materials were filtered, which were washed with hydrous methanol (containing 20% of water) and methanol, and dried under reduced pressure to give methyl 5-nitrosalicylate (38.5g, 195mmol, 72%).

¹H-NMR (CDCl₃) δ: 4.04 (3H, s), 7.10 (1H, d, J=9.5Hz), 8.35 (1H, dd, J=2.7, 9.5Hz), 8.81 (1H, d, J=2.7Hz), 11.45 (1H, s, OH).

Reference Example 256

In DMF (50ml) was dissolved methyl 5-nitrosalicylate (1.97g, 10.0mmol), and to the mixture were added ethyl 4-bromobutyrate (1.57ml, 11.0mmol) and potassium carbonate (2.76g, 20.0mmol). The mixture was stirred at 110°C for 5 hours, and the mixture was concentrated under reduced pressure. To the residue was added ethyl acetate, and the mixture was washed with water and 10% potassium carbonate solution. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica

gel 30g, ethyl acetate/hexane=1/5→1/3), and the desired fraction was concentrated under reduced pressure to give ethyl 4-(2-methoxycarbonyl-4-nitrophenoxy)butyrate (2.51g, 8.06mmol, 81%).

- 5 ¹H-NMR (CDCl₃) δ: 1.26 (3H, t, J=7.2Hz), 2.1-2.3 (2H, m), 2.60 (2H, t, J=7.1Hz), 3.93 (3H, s), 4.15 (2H, q, J=7.2Hz), 4.23 (2H, t, J=6.1Hz), 7.06 (1H, d, J=9.4Hz), 8.35 (1H, dd, J=2.8, 9.4Hz), 8.71 (1H, d, J=2.8Hz).

Reference Example 257

- 10 In THF (25ml) was dissolved ethyl 4-(2-methoxycarbonyl-4-nitrophenoxy)butyrate (2.37g, 7.61mmol), and to the mixture was added 10% palladium-carbon (containing 50% water, 0.94g). The mixture was subjected to catalytic reduction at room temperature for 4 hours. Insoluble
15 materials were filtered off, and the filtrate was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give ethyl 4-(4-amino-2-methoxycarbonyl-phenoxy)butyrate (2.20g).

IR (KBr): 1730 cm⁻¹.

- 20 ¹H-NMR (CDCl₃) δ: 1.25 (3H, t, J=7.2Hz), 2.0-2.2 (2H, m), 2.56 (2H, t, J=7.3Hz), 3.88 (3H, s), 4.00 (2H, t, J=6.0Hz), 4.14 (2H, q, J=7.2Hz), 6.75-6.9 (2H, m), 7.1-7.2 (1H, m).

Reference Example 258

- A mixture of ethyl 4-(4-amino-2-methoxycarbonyl-phenoxy)butyrate (2.20g), bis(2-chloroethyl)ether
25 (0.915ml, 7.81mmol), potassium carbonate(3.24g, 23.4mmol), sodium iodide (2.34g, 15.6mmol) and DMF (20ml) was stirred at 70°C for 24 hours, and the mixture was concentrated under reduced pressure. To the residue was added water, and the
30 mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 30g, ethyl acetate/hexane=1/4), and the desired fraction was concentrated
35 under reduced pressure to give ethyl 4-(2-methoxycarbonyl-4-morpholinophenoxy)butyrate (2.18g).

IR (KBr): 1732 cm^{-1} .

^1H -NMR (CDCl_3) δ : 1.25 (3H, t, $J=7.1\text{Hz}$), 2.0-2.2 (2H, m), 2.57 (2H, t, $J=7.1\text{Hz}$), 3.0-3.15 (4H, m), 3.8-3.9 (4H, m), 3.89 (3H, s), 4.04 (2H, t, $J=6.0\text{Hz}$), 4.14 (2H, q, $J=7.1\text{Hz}$), 6.92 (1H, d, $J=9.0\text{Hz}$), 7.04 (1H, dd, $J=3.1, 9.0\text{Hz}$), 7.36 (1H, d, $J=3.1\text{Hz}$).

Reference Example 259

In THF (15ml) was dissolved diisopropylamine (1.018ml), and to the mixture was added dropwise at 0°C n-butyl lithium (4.2ml). The mixture was stirred at the same temperature for 30 minutes. To the mixture was added dropwise a solution of ethyl 4-(2-methoxycarbonyl-4-morpholinophenoxy)butyrate (1829mg, 5.18mmol) in THF (5ml) at -78°C , ice bath was removed, and the mixture was stirred for 7 hours. To the mixture was added at 0°C 10% ammonium chloride solution (30ml), and the mixture was extracted with ethyl acetate (30ml \times 3). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 50g, ethyl acetate/hexane=1/5), and the desired fraction was concentrated under reduced pressure to give ethyl 7-morpholino-5-oxo-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylate (924mg, 2.89mmol, 56%).

Reference Example 260

In THF (10ml) was dissolved ethyl 7-morpholino-5-oxo-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylate (924mg, 2.89mmol), and to the mixture was added at -30°C a solution of sodium borohydride (164mg, 4.34mmol) in methanol (3ml). The mixture was stirred at -20°C to -15°C for 30 minutes, and the mixture was cooled to -50°C , to which was added water (15ml). The mixture was extracted with ethyl acetate (15ml \times 3), and the organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in THF (10ml), and to the mixture were added at 0°C triethylamine (2.02ml,

14.5mmol) and methanesulfonylchloride (0.336ml, 4.34mmol). The mixture was stirred at room temperature for 17 hours and concentrated under reduced pressure. To the residue was added water (15ml), and the mixture was extracted with ethyl acetate (20ml×3). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 30g, ethyl acetate/hexane=1/5), and the desired fraction was concentrated under reduced pressure to give ethyl 7-morpholino-2,3-dihydro-1-benzoxepine-4-carboxylate (691mg, 2.28mmol, 79%).
IR (KBr): 1703 cm^{-1} .
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, t, $J=7.2\text{Hz}$), 2.9-3.0 (2H, m), 3.05-3.15 (4H, m), 3.8-3.9 (4H, m), 4.22 (2H, t, $J=4.8\text{Hz}$), 4.28 (2H, q, $J=7.2\text{Hz}$), 6.8-7.0 (3H, m), 7.54 (1H, s).
Reference Example 261

In methanol (8ml) was dissolved ethyl 7-morpholino-2,3-dihydro-1-benzoxepine-4-carboxylate (800mg, 2.64mmol), and to the mixture was added 1N sodium hydroxide solution (8ml). The mixture was stirred at room temperature for 12 hours, and to the mixture was added 1N hydrochloric acid (8ml). The organic solvent was evaporated under reduced pressure, and the precipitated insoluble materials were filtered, which were washed with water and diisopropylether and dried under reduced pressure to give 7-morpholino-2,3-dihydro-1-benzoxepine-4-carboxylic acid (649mg, 2.36mmol, 89%).
 $^1\text{H-NMR}$ (CDCl_3) δ : 2.97 (2H, t, $J=4.5\text{Hz}$), 3.05-3.15 (4H, m), 3.8-3.95 (4H, m), 4.25 (2H, t, $J=4.5\text{Hz}$), 6.8-7.0 (3H, m), 7.67 (1H, s).

Reference Example 262

A mixture of 4-nitrobenzylamine (6.09g, 40.0mmol), 2-chloropyrimidine (4.82g, 42.1mmol), triethylamine (11.2ml, 80.4mmol) and ethanol (120ml) was stirred at 110°C for 24 hours, and the mixture was concentrated under reduced pressure. To the residue was added water, and the mixture

was extracted with ethyl acetate-THF. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-ethanol to give N-(4-nitrobenzyl)-N-(2-

5 pyrimidinyl)amine (0.99g, 4.3mmol, 11%).
¹H-NMR (CDCl₃) δ: 4.77 (2H, d, J=6.4Hz), 5.59 (1H, m), 6.62 (1H, t, J=4.9Hz), 7.51 (2H, d, J=8.6Hz), 8.19 (2H, d, J=8.6Hz), 8.30 (2H, d, J=4.9Hz).

Reference Example 263

10 In THF (20ml) and methanol (20ml) was dissolved N-(4-nitrobenzyl)-N-(2-pyrimidinyl)amine (921mg, 4.00mmol), and to the mixture were added at 0°C nickel bromide (137mg) and sodium borohydride (955mg). The mixture was stirred at room temperature for 30 minutes and
15 concentrated under reduced pressure. To the residue were added ethyl acetate, THF and water, and the insoluble materials were filtered off. The aqueous layer was extracted with ethyl acetate-THF, and the organic layer was dried with anhydrous sodium sulfate and concentrated under
20 reduced pressure. The residue was purified with column chromatography (silica gel 30g, ethyl acetate/hexane=1/1), and the desired fraction was concentrated under reduced pressure. To the residue was added diethylether, and the insoluble materials were filtered, which were washed with
25 diethylether and dried under reduced pressure to give 4-[N-(2-pyrimidinyl)aminomethyl]aniline (208mg, 1.04mmol, 26%).

¹H-NMR (CDCl₃) δ: 4.50 (2H, d, J=5.4Hz), 5.32 (1H, m), 6.54 (1H, t, J=4.7Hz), 6.66 (2H, d, J=8.3Hz), 7.15 (2H, d, J=8.3Hz), 8.29 (2H, d, J=4.7Hz).

Reference Example 264

A mixture of methyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (1416mg, 5.00 mmol), zinc cyanide (352mg, 3.00mmol), tetrakis(triphenylphosphine)-
35 palladium (347mg, 0.30mmol) and DMF (10ml) was stirred at 80°C for 3 hours. The mixture was concentrated under

reduced pressure, and to the residue was added ethyl acetate. Insoluble materials were filtered off, which were washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The resulting crude product was

- 5 recrystallized from ethyl acetate to give methyl 7-cyano-2,3-dihydro-1-benzoxepine-4-carboxylate (800mg, 3.49mmol, 70%).

IR (KBr): 2222, 1721 cm^{-1} .

- $^1\text{H-NMR}$ (CDCl_3) δ : 2.95-3.1 (2H, m), 3.84 (3H, s), 4.3-4.4 (2H, m), 7.05 (1H, d, $J=8.8\text{Hz}$), 7.50 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.52 (1H, s), 7.66 (1H, d, $J=2.0\text{Hz}$).

Reference Example 265

- In toluene (15ml) was suspended methyl 7-cyano-2,3-dihydro-1-benzoxepine-4-carboxylate (642mg, 2.80mmol), and to the mixture were added trimethylsilyl-azide (0.929ml, 7.00mmol) and dibutyl tin oxide (70mg, 0.28mmol). The mixture was stirred at 100°C for 24 hours and concentrated under reduced pressure. To the residue was added methanol, and the mixture was concentrated under reduced pressure. To the residue was added ethyl acetate, and the mixture was extracted with saturated sodium bicarbonate solution (30ml, 10ml \times 2). To the aqueous layer was added 6N hydrochloric acid to make the solution about pH 1, and the mixture was extracted with ethyl acetate and THF ((30ml/50ml) and (10ml/10ml) \times 2). The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure, to the residue was added ethyl acetate. Insoluble materials were filtered, which were washed with ethyl acetate and dried under reduced pressure to give methyl 7-(1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (662mg, 2.43mmol, 87%).
- $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.85-3.0 (2H, m), 3.78 (3H, s), 4.25-4.4 (2H, m), 7.21 (1H, d, $J=8.6\text{Hz}$), 7.60 (1H, s), 7.94 (1H, dd, $J=2.1, 8.6\text{Hz}$), 8.16 (1H, d, $J=2.1\text{Hz}$).

35 Reference Example 266

In DMF (6ml) was dissolved methyl 7-(1H-tetrazol-

mixture was added 1N sodium hydroxide solution (3.4ml). The mixture was stirred at 50°C for 4 hours, and to the mixture was added, under ice-cooling, 1N hydrochloric acid(3.4ml). The mixture was concentrated under reduced pressure, and
5 to the residue was added water. Insoluble materials were filtered, which were washed with water and dried under reduced pressure to give 7-(2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (295mg, 1.08mmol, 96%).

10 Reference Example 268

In methanol (3ml) and THF (3ml) was dissolved methyl 7-(2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (76mg, 0.27mmol), and to the mixture was added 1N sodium hydroxide solution (0.8ml). The
15 mixture was stirred at 50°C for 4 hours, and to the mixture was added, under ice-cooling, 1N hydrochloric acid (0.8ml). The mixture was concentrated under reduced pressure, and to the residue was added water. Insoluble materials were filtered, which were washed with water and dried under
20 reduced pressure to give 7-(1-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (69mg, 0.25 mmol, 95%).

Reference Example 269

In THF (500ml) was dissolved 4-[(benzyloxy)carbonyl]-
25 aminobutyric acid (25.0g), and to the mixture was gradually added at -5°C methyl iodide (37.4g). Under nitrogen atmosphere, the mixture was stirred at 0°C for 15 minutes and then at room temperature for 24 hours. To the mixture was added ethyl acetate (300ml) and then water (800ml). The
30 mixture was made pH 11 with sodium hydroxide and washed with ether (400ml×2). The aqueous layer was made pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (1000ml and 500ml×3). The organic layer was washed with 1M sodium thiosulfate solution (300ml) and dried with
35 magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-[(benzyloxy)carbonyl]-4-

5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (400mg, 1.47mmol), and to the mixture was added at 0°C sodium hydride (60%, 90mg, 2.3mmol). The mixture was stirred at the same temperature for 15 minutes, and to the mixture was added
5 at 0°C methyl iodide (0.28ml, 4.4mmol). While the temperature of the mixture was warmed from 0°C to room temperature, the mixture was stirred for 3 hours. To the mixture was added at 0°C water (30ml), and the mixture was extracted with ethyl acetate. The organic layer was dried
10 with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel 40g, ethyl acetate/hexane=1/8 →1/2), and the first eluted desired fraction was concentrated under reduced pressure to give methyl 7-
15 (2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (334mg, 1.17mmol, 79%). The second eluted desired fraction was concentrated under reduced pressure to give methyl 7-(1-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (76mg, 0.27mmol, 18%).

Methyl 7-(2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate;

IR (KBr): 1705 cm⁻¹.

¹H-NMR (CDCl₃) δ: 2.95-3.1 (2H, m), 3.83 (3H, s), 4.25-4.4 (2H, m), 4.39 (3H, s), 7.09 (1H, d, J=8.4Hz), 7.69 (1H, s),
25 8.00 (1H, dd, J=2.2, 8.4Hz), 8.15 (1H, d, J=2.2Hz).

Methyl 7-(1-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate;

IR (KBr): 1705 cm⁻¹.

¹H-NMR (CDCl₃) δ: 3.0-3.1 (2H, m), 3.84 (3H, s), 4.3-4.45 (2H, m), 4.20 (3H, s), 7.17 (1H, d, J=8.4Hz), 7.61 (1H, s), 7.63 (1H, dd, J=2.2, 8.4Hz), 7.75 (1H, d, J=2.2Hz).

Reference Example 267

In methanol (7ml) and THF (7ml) was suspended methyl
35 7-(2-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1-benzoxepine-4-carboxylate (324mg, 1.13mmol), and to the

methyl-aminobutyric acid (26.3g).

¹H NMR (200MHz, CDCl₃) δ 1.88 (2H, m), 2.35-2.37 (2H, m), 2.93 (3H, s), 3.36 (2H, t, J=6.6Hz), 5.13 (2H, s), 7.35 (5H, s).

5 Reference Example 270

To dichloromethane (1000ml) was added at room temperature anhydrous magnesium sulfate (50.6g) and then concentrated sulfuric acid (6.0ml). The mixture was stirred at room temperature for 15 minutes, and to the
10 mixture was added 4-[(benzyloxy)carbonyl]-4-methyl-aminobutyric acid (26.3g) and then tert-butanol (50.5ml). The mixture was sealed completely and stirred at room temperature for 18 hours. To the mixture was added saturated sodium hydrogen carbonate solution to dissolve
15 all of the magnesium sulfate, and the mixture was stirred. The organic layer was separated, washed with saturated brine (400ml) and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography
20 (250g, hexane:ethyl acetate=5:1) to give tert-butyl 4-[(benzyloxy)-carbonyl]-4-methylaminobutyrate (17.2g, 53%).

¹H NMR (200MHz, CDCl₃) δ 1.44 (9H, s), 1.82 (2H, quint, J=6.6Hz), 2.21 (2H, t, J=6.2Hz), 2.93 (3H, s), 3.31 (2H, t, J=7.1Hz), 5.13 (2H, s), 7.35 (5H, s).

25 Reference Example 271

In methanol (70ml) was dissolved tert-butyl 4-[(benzyloxy)carbonyl]-4-methylaminobutyrate (6.06g), and to the mixture was added 10% palladium-carbon (580mg).
30 Under hydrogen atmosphere, the mixture was stirred at room temperature for 3 hours, and 10% palladium-carbon was removed. The solvent was evaporated under reduced pressure to give tert-butyl 4-methylaminobutyrate (3.35g, 98%).
¹H NMR (200MHz, CDCl₃) δ 1.45 (9H, s), 1.72 (1H, brs), 1.77
35 (2H, quint, J=7.2Hz), 2.27 (2H, t, J=7.3Hz), 2.43 (3H, s), 2.61 (2H, t, J=7.1Hz).

Reference Example 272

In DMF (5.0ml) was dissolved tert-butyl 4-methyl-aminobutyrate (1050mg), and to the mixture was added at room temperature a solution of 5-bromo-2-fluorobenzaldehyde (1025mg) in DMF (1.0ml) and then potassium carbonate (837mg). The mixture was stirred at 70°C for 60 hours, and to the mixture was added at room temperature water (50ml). The mixture was extracted with ethyl acetate (50ml×3), and the organic layer was washed with saturated brine (50ml×3) and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, hexane:ethyl acetate=10:1) to give tert-butyl 4-(4-bromo-2-formyl-N-methylanilino) butyrate (1620mg, 90%).

¹H NMR (200MHz, CDCl₃) δ 1.42 (9H, s), 1.88 (2H, quint, J=7.4Hz), 2.22 (2H, t, J=7.3Hz), 2.88 (3H, s), 3.14 (2H, t, J=7.3Hz), 7.01 (1H, d, J=8.6Hz), 7.55 (1H, dd, J=8.7, 2.5Hz), 7.88 (1H, d, J=2.6Hz), 10.19 (1H, s).

Reference Example 273

In tert-butanol (250ml) was dissolved tert-butyl 4-(4-bromo-2-formyl-N-methylanilino)butyrate (4.54g) and tert-butoxy potassium (1.43g), and the mixture was refluxed for 1 hour and cooled. To the mixture was added water (500ml), and the mixture was extracted with ethyl acetate (500ml×2). The aqueous layer was made weakly acidic with 1N hydrochloric acid (about 12.5ml), and the mixture was extracted with ethyl acetate (500ml). Both of these organic layer was washed with saturated brine (250ml) and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (200g, hexane:ethyl acetate=10:1→1:1) to give tert-butyl 7-bromo-1-methyl-2,3-dihydro-1-benzoazepine-4-carboxylate (3.33g, 77%) and 7-bromo-1-methyl-2,3-dihydro-1H-1-benzoazepine-4-carboxylic acid (0.60g, 17%).

tert-butyl 7-bromo-1-methyl-2,3-dihydro-1-benzoazepine-4-carboxylate;

¹H NMR (200MHz, CDCl₃) δ 1.53 (9H, s), 2.80 (2H, t, J=4.8Hz), 3.00 (3H, s), 3.21 (2H, t, J=4.7Hz), 6.65 (1H, d, J=8.8Hz),
5 7.25 (1H, dd, J=8.8, 2.2Hz), 7.39 (1H, d, J=2.6Hz), 7.46 (1H, s).

7-bromo-1-methyl-2,3-dihydro-1H-1-benzoazepine-4-carboxylic acid;

¹H NMR (200MHz, CDCl₃) δ 2.85 (2H, t, J=4.8Hz), 3.03 (3H, s), 3.25 (2H, t, J=4.9Hz), 6.67 (1H, d, J=9.2Hz), 7.29 (1H, dd, J=8.8, 2.2Hz), 7.44 (1H, d, J=2.6Hz), 7.67 (1H, s).
10 Reference Example 274

In water:ethanol:toluene (1:1:10, 18.0ml) were dissolved 4-methylphenyl borate (276mg) and tert-butyl
15 7-bromo-1-methyl-2,3-dihydro-1-benzoazepine-4-carboxylate (571mg), and to the mixture was added potassium carbonate (560mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis(triphenyl)phosphine palladium (78mg). Under argon
20 atmosphere, the mixture was refluxed for 19.5 hours. The mixture was diluted with ethyl acetate (300ml) and washed with water (100ml) and saturated brine (100ml). The organic layer was dried with anhydrous magnesium sulfate. The
25 solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (120g, hexane→hexane:ethyl acetate=10:1) to give tert-butyl 1-methyl-7-(4-methylphenyl)-2,3-dihydro-1-benzoazepine-4-carboxylate (422mg, 72%).

¹H NMR (200MHz, CDCl₃) δ 1.54 (9H, s), 2.38 (3H, s), 2.83 (2H, t, J=4.9Hz), 3.06 (3H, s), 3.28 (2H, t, J=4.9Hz), 6.85 (1H, d, J=8.4Hz), 7.23 (2H, d, J=8.0Hz), 7.447 (1H, dd, J=8.6, 2.4Hz), 7.463 (2H, d, J=8.2Hz), 7.53 (1H, d, J=2.2Hz), 7.67 (1H, s).

Reference Example 275

35 In ethyl acetate (7.0ml) was dissolved tert-butyl 1-methyl-7-(4-methylphenyl)-2,3-dihydro-1-benzoazepine-

- 4-carboxylate (490mg), and to the mixture was added 4N hydrochloric acid (ethyl acetate) (7.0ml). The mixture was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure, and the residue was washed with hexane (10ml×3) to give 1-methyl-7-(4-methylphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid hydrochloride (443mg, 96%).
- mp 249-252°C (decomp.).
- ¹H NMR (200MHz, DMSO-d₆) δ 2.32 (3H, s), 2.75 (2H, t, J=4.6Hz), 3.03 (3H, s), 3.25 (2H, t, J=4.9Hz), 6.92 (1H, d, J=8.6Hz), 7.22 (2H, d, J=8.2Hz), 7.53 (1H, dd, J=8.8, 2.4Hz), 7.55 (2H, d, J=8.2Hz), 7.65 (1H, d, J=2.4Hz), 7.68 (1H, s).
- IR (KBr) 3021, 2469, 1707, 1466, 1190, 1107, 810, 530 cm⁻¹.
- Anal. Calcd. for C₁₉H₁₉NO₂·HCl·0.3H₂O:
C, 68.08; H, 6.19; N, 4.18.
Found: C, 67.97; H, 6.13; N, 4.05.

Reference Example 276

- In DMF (12.0ml) was dissolved 7-bromo-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylic acid hydrochloride (600mg), and to the mixture was added thionyl chloride (0.39ml). The mixture was stirred at room temperature for 15 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (14.0ml). The thus obtained acid chloride solution was added dropwise at 0°C to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (562mg) and triethylamine (1.48ml) in dichloromethane (5.5ml). The mixture was stirred at 0°C for 10 minutes and then at room temperature for 5 hours. To the mixture was added water (100ml), and the mixture was extracted with dichloromethane (100ml×3). The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (150g, ethyl acetate:ethanol=10:1) to give 7-bromo-1-methyl-N-[4-

[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]-phenyl]-2,3-dihydro-1-benzoxepine-4-carboxamide (767mg, 75%).

mp 62-64°C.

- 5 ¹H NMR (200MHz, CDCl₃) δ 1.63-1.79 (4H, m), 2.21 (3H, s), 2.57-2.72 (1H, m), 2.94 (2H, t, J=4.2Hz), 3.03 (3H, s), 3.27-3.44 (2H + 2H, m), 3.57 (2H, s), 4.00-4.07 (2H, m), 6.70 (1H, d, J=8.8Hz), 7.20 (1H, s), 7.26-7.303 (2H, m), 7.301 (1H, dd, J=8.6, 2.4Hz), 7.42 (1H, d, J=2.6Hz),
10 7.50-7.55 (1H + 2H, m).

IR (KBr) 3264, 2949, 2843, 1655, 1597, 1514, 1499, 1406, 1314, 1246, 1182, 810 cm⁻¹.

Anal. Calcd. for C₂₅H₃₀N₃O₂Br·0.25H₂O:

C, 61.41; H, 6.29; N, 8.59.

- 15 Found: C, 61.45; H, 6.25; N, 8.32.

Working Example 310 (Production of Compound 310)

- In hydrous methanol was dissolved N,N-dimethyl-N-(4-(((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)amino)benzyl)tetrahydro-2H-pyran-4-aminium
20 iodide (14.2g), and the mixture was subjected to ion exchange resin (DOWEX SBR, 20-50 mesh, Cl⁻ type) column and eluted with hydrous methanol. The solvent of the resulting fraction was evaporated, and to the residue was added acetone to give crude crystals, which were recrystallized from
25 ethanol to give N,N-dimethyl-N-(4-(((7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl)carbonyl)-amino)benzyl)-tetrahydro-2H-pyran-4-aminium chloride (Compound 310) (10.4g) as colorless crystals.

mp 232-237°C(dec.).

- 30 ¹H-NMR(δ ppm, DMSO-d₆) 1.76-2.00 (2H, m), 2.14-2.20 (2H, m), 2.35 (3H, s), 2.89 (6H, s), 3.01 (2H, t, J=4.5Hz), 3.29-3.46 (2H, m), 3.55-3.69 (1H, m), 4.04-4.09 (2H, m), 4.31 (2H, t, J=4.5Hz), 4.50 (2H, s), 7.06 (1H, d, J=8.4Hz), 7.27 (2H, d, J=8.4Hz), 7.46 (1H, s), 7.53-7.59 (5H, m), 7.79 (1H, d, J=2.2Hz), 7.92 (2H, d, J=8.4Hz), 10.34 (1H, s).

IR(KBr) ν: 2973, 2849, 1645, 1516cm⁻¹.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_3$:

C, 72.10; H, 7.00; N, 5.25; Cl, 6.65.

Found C, 72.03; H, 6.83; N, 5.38; Cl, 6.47.

Working Example 311 (Production of Compound 311)

- 5 In dichloromethane (5ml) was suspended 7-(4-methyl-phenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.25g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.16ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for
- 10 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and the mixture was added dropwise to a solution of 4-((N,N-bis(2-methoxy-ethyl)amino)methyl)aniline (0.24g) and triethylamine (0.4ml) in tetrahydrofuran (10ml) under ice-cooling.
- 15 Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer washed with water and saturated brine, and dried with anhydrous magnesium sulfate.
- 20 Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N,N-bis(2-methoxyethyl)-amino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-
- 25 benzoxepine-4-carboxamide (Compound 311) (0.25g) as colorless crystals.

mp 110-112°C.

- $^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.39 (3H, s), 2.74 (4H, t, $J=6.0\text{Hz}$), 3.07 (2H, t, $J=4.4\text{Hz}$), 3.32 (6H, s), 3.48 (4H, t, $J=6.0\text{Hz}$), 3.69 (2H, s), 4.35 (2H, t, $J=4.4\text{Hz}$), 7.05 (1H, d, $J=8.0\text{Hz}$), 7.24 (2H, d, $J=8.4\text{Hz}$), 7.33 (2H, d, $J=8.8\text{Hz}$), 7.43-7.55 (6H, m), 7.61 (1H, s).
- 30

IR(KBr) ν : 3287, 2876, 1651 cm^{-1} .

Anal. Calcd. for $C_{31}H_{36}N_2O_4$:

- 35 C, 74.37; H, 7.25; N, 5.60.

Found C, 74.33; H, 7.15; N, 5.45.

Working Example 312 (Production of Compound 312)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.25g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.23ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and the mixture was added dropwise to a solution of 4-((N-(3-ethoxypropyl)-N-methylamino)methyl)aniline dihydrochloride (0.3g) and triethylamine (0.62ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-(3-ethoxypropyl)-N-methylamino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 312) (0.3g) as colorless crystals.

mp. 119-122°C.

¹H-NMR(δ ppm, CDCl₃) 1.19 (3H, t, J=7.1Hz), 1.65-1.85 (2H, m), 2.19 (3H, s), 2.39 (3H, s), 2.46 (2H, t, J=7.2Hz), 3.08 (2H, t, J=4.8Hz), 3.42-3.52 (6H, m), 4.36 (2H, t, J=4.8Hz), 7.06 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.0Hz), 7.30 (2H, d, J=8.8Hz), 7.44-7.58 (7H, m).

IR(KBr) ν: 2975, 2872, 1647, 1516cm⁻¹.

Anal. Calcd. for C₃₁H₃₆N₂O₃:

C, 76.83; H, 7.49; N, 5.78.

Found C, 76.73; H, 7.31; N, 5.95.

35 Working Example 313 (Production of Compound 313)

In THF (5ml) was dissolved 7-(4-methylphenyl)-2,3-

dihydro-1-benzoxepine-4-carboxylic acid (0.25g), and to the mixture were added, under ice-cooling, oxalyl chloride (0.16ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and
5 the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the mixture was added dropwise to a solution of 4-((N-(1,3-dimethoxypropan-2-yl)-N-methylamino)methyl)aniline (0.23g) and triethylamine (0.5ml) in tetrahydrofuran (10ml), under ice-cooling.
10 Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer washed with water and saturated brine, and dried with anhydrous magnesium sulfate.
15 Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-(1,3-dimethoxypropan-2-yl)-N-methylamino)methyl)-
20 phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 313) (0.25g) as colorless crystals. mp 128-132°C.
¹H-NMR(δ ppm, CDCl₃) 2.31 (3H, s), 2.39 (3H, s), 3.00-3.09 (3H, m), 3.35 (6H, s), 3.44-3.63 (4H, m), 3.71 (2H, s), 4.35
25 (2H, t, J=4.7Hz), 7.05 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.0Hz), 7.33 (2H, d, J=8.8Hz), 7.43-7.58 (7H, m).
IR(KBr) ν: 3285, 2882, 1651, 1516cm⁻¹.

Anal. Calcd. for C₃₁H₃₆N₂O₄:

C, 74.37; H, 7.25; N, 5.60.

30 Found C, 74.17; H, 7.05; N, 5.75.

Working Example 314 (Production of Compound 314)

In THF (5ml) was dissolved 7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylic acid (0.25g), and to the mixture were added, under ice-cooling, oxalyl chloride
35 (0.16ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and

the solvent was evaporated. The residue was dissolved in tetrahydrofuran (15ml), and the mixture was added dropwise to a solution of 4-((N-(2-methoxyethyl)-N-methylamino)-methyl)aniline (0.21g) and triethylamine (0.37ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-(2-methoxyethyl)-N-methylamino)methyl)phenyl)-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 314) (0.24g) as colorless crystals. mp 121-122°C.

¹H-NMR (δ ppm, CDCl₃) 2.26 (3H, s), 2.39 (3H, s), 2.60 (2H, t, J=5.8Hz), 3.07 (2H, t, J=4.5Hz), 3.35 (3H, s), 3.49-3.54 (4H, m), 4.35 (2H, t, J=4.5Hz), 7.05 (1H, d, J=8.4Hz), 7.24 (2H, d, J=8.8Hz), 7.31 (2H, d, J=8.8Hz), 7.43-7.56 (6H, m), 7.62 (1H, s).

IR(KBr) ν: 3287, 2926, 1651, 1516cm⁻¹.

Anal. Calcd. for C₂₉H₃₂N₂O₃:

C, 76.29; H, 7.06; N, 6.14.

Found C, 75.99; H, 7.02; N, 6.22.

Working Example 315 (Production of Compound 315)

In water/ethanol/toluene(1:1:10, 18.0ml) were dissolved 4-trifluoromethoxyphenyl borate (208mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (407mg), and to the mixture was added potassium carbonate (279mg). Under argon atmosphere, the mixture was stirred for 30 minutes, and the mixture was added tetrakis(triphenyl)phosphine palladium (39mg). Under

- argon atmosphere, the mixture was refluxed for 16 hours, and the mixture was diluted with ethyl acetate (200ml). The mixture was washed with water (50ml) and saturated brine (50ml), and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, ethyl acetate→ethyl acetate/ethanol=20:1) and recrystallized from ethanol to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-trifluoromethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 315) (148mg, 31%).
- mp 182-183°C.
- ¹H NMR (200MHz, CDCl₃) δ 1.63-1.76 (4H, m), 2.20 (3H, s), 2.56-2.72 (1H, m), 2.96 (2H, t, J=4.6Hz), 3.09 (3H, s), 3.30-3.43 (4H, m), 3.56 (2H, s), 4.01-4.06 (2H, m), 6.89 (1H, d, J=8.6Hz), 7.25 (2H, d, J=8.2Hz), 7.30 (2H, d, J=8.6Hz), 7.40 (1H, s), 7.48 (1H, dd, J=8.6, 2.4Hz), 7.51-7.58 (6H, m).
- IR (KBr) 2951, 2847, 1651, 1514, 1501, 1260, 1221, 1163, 806, 733 cm⁻¹.
- Anal. Calcd. for C₃₂H₃₄N₃O₃F₃: C, 67.95; H, 6.06; N, 7.43.
Found: C, 67.74; H, 5.87; N, 7.68.
- Working Example 316 (Production of Compound 316)
- In water/ethanol/toluene (1:1:10, 18.0ml) were dissolved 4-(1-piperidinyl)phenyl borate (179mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (353mg), and to the mixture was added potassium carbonate (242mg). Under argon atmosphere, the mixture was stirred for 40 minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (34mg). Under argon atmosphere, the mixture was refluxed for 15 hours, and the mixture was diluted with ethyl acetate (200ml). The mixture was washed with water (50ml) and saturated brine (50ml), and the organic layer was dried with anhydrous magnesium

sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, ethyl acetate/ethanol=9:1) and recrystallized from ethanol to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]-phenyl]-7-[4-(1-piperidinyl)phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 316) (79mg, 19%).
mp 202-204°C.

¹H NMR (200MHz, CDCl₃) δ 1.59-1.77 (10H, m), 2.21 (3H, s), 2.57-2.73 (1H, m), 2.95 (2H, t, J=4.4Hz), 3.07 (3H, s), 3.19 (4H, t, J=5.1Hz), 3.31-3.43 (4H, m), 3.57 (2H, s), 4.01-4.06 (2H, m), 6.86 (1H, d, J=8.4Hz), 6.99 (2H, d, J=8.8Hz), 7.30 (2H, d, J=8.6Hz), 7.39-7.50 (5H, m), 7.54 (2H, d, J=8.4Hz), 7.57 (1H, s).

IR (KBr) 2938, 2849, 1645, 1607, 1505, 1314, 1235, 910, 812, 733cm⁻¹.

Anal. Calcd. for C₃₆H₄₄N₄O₂: C, 76.56; H, 7.85; N, 9.92.
Found: C, 76.53; H, 7.79; N, 10.01.

Working Example 317 (Production of Compound 317)

In water/ethanol/toluene (1:1:10, 60.0ml) were dissolved 4-methylphenyl borate (658mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (2.01g), and to the mixture was added potassium carbonate (1.34g). Under argon atmosphere, the mixture was stirred for 30 minutes, and to the mixture was added tetrakis(triphenyl)phosphine palladium (186mg). Under argon atmosphere, the mixture was refluxed for 17 hours, and the mixture was dilute with ethyl acetate (750ml). The mixture was washed with water (200ml) and saturated brine (100ml), and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (150g, ethyl acetate→ethyl acetate/ethanol=20:1) and recrystallized from ethanol to give 1-formyl-7-(4-methylphenyl)-N-[4-[[N-methyl-N-

(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 317) (669mg, 33%).

mp 229-230.5°C.

5 ¹H NMR (200MHz, CDCl₃) δ 1.69-1.79 (4H, m), 2.21 (3H, s), 2.41 (3H, s), 2.57-2.72 (1H, m), 3.04 (2H, t, J=4.9Hz), 3.37 (2H, td, J=10.2, 3.1Hz), 3.57 (2H, s), 3.93 (2H, t, J=5.5Hz), 4.01-4.07 (2H, m), 7.21 (1H, d, J=8.2Hz), 7.29 (2H, d, J=7.6Hz), 7.32 (2H, d, J=8.4Hz), 7.50 (2H, d, J=8.8Hz), 7.54 (2H, d, J=8.8Hz), 7.58 (1H, s), 7.59 (1H, dd, J=8.2, 2.2Hz), 1H was concealed under 7.55-7.58, 7.71 (1H, d, J=2.2Hz), 8.56 (1H, s).

10 IR (KBr) 2946, 2847, 1667, 1597, 1516, 1497, 1360, 1316, 814, 733 cm⁻¹.

15 Anal. Calcd. for C₃₂H₃₅N₃O₃: C, 75.41; H, 6.92; N, 8.25.
Found: C, 75.45; H, 6.95; N, 8.18.

Working Example 318 (Production of Compound 318)

To 1-formyl-7-(4-methylphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (1177mg) was added 1N hydrochloric acid (20ml), and the mixture was stirred at 100°C for 1 hour. The mixture was dilute with ethyl acetate (50ml) and made weakly basic with saturated sodium hydrogen carbonate solution (45ml). To the mixture were 20 added ethyl acetate (250ml) and water (100ml), and separated. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, ethyl acetate/ethanol=9:1) to give 7-(4-methyl- 25 phenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 318) (804mg, 72%) as amorphous. ¹H NMR (200MHz, CDCl₃) δ 1.69-1.80 (4H, m), 2.21 (3H, s), 2.38 (3H, s), 2.58-2.72 (1H, m), 2.96 (2H, t, J=4.4Hz), 3.37 (2H, td, J=11.4, 3.1Hz), 3.47 (2H, t, J=4.8Hz), 3.57 (2H, s), 4.01-4.07 (2H, m), 4.53-4.70 (1H, br), 6.71 (1H, d,

J=8.4Hz), 7.22 (2H, d, J=7.8Hz), 7.28-7.32 (4H, m), 7.35 (1H, dd, J=8.4, 2.2Hz), 7.42 (1H, s), 7.46 (1H, s), 7.48 (1H, d, J=2.0Hz), 7.54 (2H, d, J=8.6Hz).

IR (KBr) 3330, 2949, 2847, 1651, 1609, 1514, 1507, 1408,

5 1316, 910, 812, 735 cm^{-1} .

Anal. Calcd. for $\text{C}_{31}\text{H}_{35}\text{N}_3\text{O}_2$: C, 77.31; H, 7.32; N, 8.72.

Found: C, 77.44; H, 7.12; N, 8.78.

Working Example 319 (Production of Compound 319)

10 In dimethylformamide (5ml) was dissolved 7-(4-ethoxyphenyl)-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylic acid hydrochloride (0.5g), and to the mixture was added, under ice-cooling, thionyl chloride (0.25ml). The mixture was stirred at room temperature for 45 minutes, and the solvent was evaporated. The residue was dissolved
15 in tetrahydrofuran (15ml), and the mixture was added dropwise to a suspension of 4-((N-(3-ethoxypropyl)-N-methylamino)methyl)aniline dihydrochloride (0.41g) and triethylamine (1.2ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was
20 stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the
25 solvent was evaporated, and the residue was purified with silica gel column (methanol/triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give N-(4-((N-(3-ethoxypropyl)-N-methylamino)methyl)phenyl)-7-(4-ethoxyphenyl)-1-methyl-
30 2,3-dihydro-1-benzazepine-4-carboxamide (Compound 319) (0.39g) as pale yellow crystals.
mp 129-131°C.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 1.19 (3H, t, J=6.9Hz), 1.44 (3H, t, J=7.1Hz), 1.76-1.84 (2H, m), 2.19 (3H, s), 2.46 (2H, t, J=7.4Hz), 2.97 (2H, t, J=4.6Hz), 3.09 (3H, s), 3.35 (2H, t, J=4.8Hz), 3.41-3.52 (6H, m), 4.07 (2H, q, J=7.1Hz), 6.88

(1H, d, J=8.4Hz), 6.95 (2H, d, J=8.8Hz), 7.29 (2H, d, J=8.8Hz), 7.40-7.55 (8H, m).

IR(KBr) ν : 2978, 2868, 1651, 1607, 1516, 1503cm⁻¹.

Anal. Calcd. for C₃₃H₄₁N₃O₃:

5 C, 75.11; H, 7.83; N, 7.96.

Found C, 74.90; H, 7.98; N, 7.97.

Working Example 320 (Production of Compound 320)

In water/ethanol/toluene (1:1:10, 18.0ml) were dissolved 4-ethylthiophenyl borate (264mg) and 7-bromo-10 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (439mg), and to the mixture was added potassium carbonate (301mg). Under argon atmosphere, the mixture was stirred for 30 minutes, and to the mixture was added 15 tetrakis(triphenyl)phosphine palladium (42mg). Under argon atmosphere, the mixture was refluxed for 17.5 hours, and the mixture was dilute with ethyl acetate (200ml). The mixture was washed with water (50ml) and saturated brine (50ml), and the organic layer was dried with anhydrous 20 magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, ethyl acetate→ethyl acetate/ethanol=9:1) and recrystallized from ethanol to give 7-(4-ethylthiophenyl)-1-methyl-N-[4-[[N-methyl-N-25 (tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 320) (168mg, 34%).

mp 139-141°C.

¹H NMR (200MHz, CDCl₃) δ 1.34 (3H, t, J=7.3Hz), 1.63-1.76 30 (4H, m), 2.21 (3H, s), 2.57-2.72 (1H, m), 2.98 (2H, q, J=7.3Hz), 2H around δ 2.96 was concealed by δ 2.98, 3.10 (3H, s), 3.31-3.43 (4H, m), 3.57 (2H, s), 4.00-4.07 (2H, m), 6.89 (1H, d, J=8.6Hz), 7.28-7.40 (6H, m), 7.466 (1H, dd, J=8.5, 2.3Hz), 7.473 (1H, s), 7.52-7.56 (4H, m).

35 IR (KBr) 2948, 2845, 1645, 1597, 1514, 1489, 1408, 1314, 1244, 1188, 812 cm⁻¹.

Anal. Calcd. for $C_{23}H_{19}N_3O_2S$: C, 73.16; H, 7.26; N, 7.76.

Found: C, 72.96; H, 7.08; N, 7.64.

Working Example 321 (Production of Compound 321)

In DMF (10.0ml) was dissolved 7-(4-methylphenyl)-1-
5 [(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-
4-carboxylic acid (387mg), and to the mixture was added
thionyl chloride (0.175ml). The mixture was stirred at room
temperature for 1 hour, and excess thionyl chloride and DMF
were evaporated under reduced pressure. The residue was
10 dissolved in dichloromethane (10.0ml), and the mixture was
added dropwise to a solution of 4-[[N-methyl-N-
(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline
dihydrochloride (331mg) and triethylamine (0.98ml) in
dichloromethane (15.0ml) at 0°C. The mixture was stirred
15 at room temperature for 4 hours, and to the mixture was added
water (50ml). The mixture was extracted with
dichloromethane (100ml \times 3), and the organic layer was
dried with anhydrous magnesium sulfate. The solvent was
evaporated under reduced pressure, and the residue was
20 purified with silica gel column chromatography (35g, ethyl
acetate \rightarrow ethyl acetate/ethanol=9:1) and recrystallized
from ethanol to give 7-(4-methylphenyl)-N-[4-[[N-
methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]-
phenyl]-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-
25 benzazepine-4-carboxamide (Compound 71) (251mg, 43%).
mp 185-187°C.

1H NMR (200MHz, $CDCl_3$) δ 1.70-1.77 (4H, m), 2.21 (3H, s),
2.41 (3H, s), 2.57-2.72 (1H, m), 3.11 (2H, t, $J=5.9Hz$), 3.37
(2H, td, $J=11.3, 2.9Hz$), 3.58 (2H, s), 4.02-4.08 (4H, m),
30 7.26-7.35 (4H, m), 7.46-7.61 (8H, m), 7.64 (1H, s).

IR (KBr) 1661, 1516, 1497, 1393, 1314, 1223, 1194, 1142,
812 cm^{-1} .

Anal. Calcd. for $C_{32}H_{34}F_3N_3O_4S$: C, 62.63; H, 5.58; N, 6.85.

Found: C, 62.58; H, 5.57; N, 6.91.

35 Working Example 322 (Production of Compound 322)

To a solution of 7-(4-methylphenyl)-2,3-

dihydrobenzoxepine-4-carboxylic acid (280mg) and 2-[(4-aminophenyl)methylamino]pyridine (199mg) in DMF (4ml) was added, under ice-cooling, diethyl cyanophosphate (0.18ml) and triethylamine (0.17ml), and the mixture was stirred at 0 °C for 30 minutes and then at room temperature for 1 hour. To the mixture was added DMAP (1 piece), and the mixture was stirred at room temperature for 18 hours. Under ice-cooling, to the mixture was added sodium bicarbonate solution, and the mixture was extracted with ethyl acetate, washed with brine, dried (anhydrous magnesium sulfate) and concentrated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane =1/1) and recrystallized from ethyl acetate/hexane to give N-[4-[(pyrid-2-yl)aminomethyl]phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (Compound 72) (97mg) as colorless crystals.

m.p. 189-190°C

¹H-NMR (200MHz, CDCl₃) δ : 2.39 (3H, s), 3.07 (2H, t, J = 4.6), 4.36 (2H, t, J = 4.6), 4.49 (2H, d, J = 4.6), 4.9-5.0 (1H, brm), 6.38 (1H, d, J = 8.4), 6.60 (1H, dd, J = 5.2, 7.2), 7.06 (1H, d, J = 8.4), 7.2-7.6 (12H, m), 8.05-8.15 (1H, m).

IR (KBr) 1651, 1597, 1522, 1491, 1439, 1316, 1254, 812, 772cm⁻¹

Anal. for C₃₀H₂₇N₃O₂·0.2H₂O

Calcd. C, 77.46; H, 5.94; N, 9.03:

Found. C, 77.24; H, 5.96; N, 8.91.

Reference Example 277

A solution of p-nitrobenzyl bromide (10g) in THF (50ml) was added dropwise to a solution of bis(2-methoxyethyl)-amine (6.8g) and triethylamine (10ml) in THF (50ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium

sulfate. Under reduced pressure, the solvent was evaporated to give N,N-bis(2-methoxyethyl)-4-nitrobenzylamine (10.8g) as yellow oil.

¹H-NMR(δ ppm, CDCl₃) 2.76 (4H, t, J=5.6Hz), 3.31 (6H, s), 3.48 (4H, t, J=5.6Hz), 3.83 (2H, s), 7.54 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz).

IR(neat) ν : 2878, 1599, 1520cm⁻¹.

Reference Example 278

In acetic acid (200ml) was dissolved N,N-bis(2-methoxyethyl)-4-nitrobenzylamine (10.5g), and to the mixture was added reduced iron (11g) little by little. The mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added ethyl acetate and precipitates were filtered off. The filtrate was washed with sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate) to give 4-((N,N-bis(2-methoxyethyl)amino)-methyl)aniline (6.2g) as red oil.

¹H-NMR(δ ppm, CDCl₃) 2.71 (4H, t, J=6.3Hz), 3.31 (6H, s), 3.46 (4H, t, J=6.3Hz), 3.59 (2H, s), 6.63 (2H, d, J=8.4Hz), 7.10 (2H, d, J=8.4Hz).

IR(neat) ν : 3353, 2874, 2818, 1615cm⁻¹.

Reference Example 279

In 1,2-dichloroethane (50ml) were dissolved p-nitrobenzaldehyde (5g) and 3-ethoxypropylamine (3.75g), and to the mixture was added, under ice-cooling, triacetoxysodium boro hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and to the mixture were added, under ice-cooling, 37% formalin (3.5ml) and triacetoxysodium boro hydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 8 hours, and the solvent was evaporated. The residue was neutralized with 1N sodium hydroxide solution, and the mixture was extracted with ethyl acetate.

The organic layer was washed with water and subjected to back extraction with 1N hydrochloric acid. The mixture was washed with ethyl acetate, neutralized with 1N sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give N-(3-ethoxypropyl)-N-methyl-4-nitrobenzylamine (6.6g) as yellow oil.

¹H-NMR(δ ppm, CDCl₃) 1.18 (3H, t, J=7.0Hz), 1.72-1.86 (2H, m), 2.20 (3H, s), 2.48 (2H, t, J=7.6Hz) 3.41-3.52 (4H, m), 3.58 (2H, s), 7.50 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz). IR(neat) ν: 2859, 1520, 1346cm⁻¹.

Reference Example 280

In THF (60ml) were suspended N-(3-ethoxypropyl)-N-methyl-4-nitrobenzylamine (6.0g), iron chloride (III) (0.06g) and active charcoal (0.6g), and to the suspension was added dropwise hydrazine monohydrate (4.1ml) at 60-65°C. The mixture was stirred at 65°C for 4 hours, and to the mixture was added hydrazine monohydrate (15ml). The mixture was stirred at 65°C for 4 hours and filtered. The solvent of the filtrate was evaporated, and the residue was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was dissolved in 2-propanol, and to the mixture was added hydrochloric acid (6ml). The solvent was evaporated, and the precipitated 4-((N-(3-ethoxypropyl)-N-methylamino)-methyl)aniline dihydrochloride (5.8g) was filtered with ethyl acetate and washed with ethyl acetate-hexane to give yellow powder.

mp 173-175°C.

¹H-NMR(δ ppm, CDCl₃+CD₃OD) 1.16 (3H, t, J=7.0Hz), 2.18 (2H, br), 2.72 (3H, s), 3.05-3.29 (2H, m), 3.40-3.52 (4H, m), 4.22-4.43 (2H, m), 7.58 (2H, d, J=8.2Hz), 7.78 (2H, d, J=8.2Hz), 11.86 (1H, br).

IR(KBr) ν: 1651cm⁻¹.

Anal. Calcd. for $C_{11}H_{22}N_2O \cdot 2HCl$:

C, 52.88; H, 8.19; N, 9.49.

Found C, 52.61; H, 8.05; N, 9.55.

Reference Example 281

5 In 1,2-dichloroethane (50ml) were suspended p-nitrobenzylamine hydrochloride (3g), 1,3-dimethoxyacetone (1.9g) and triethylamine (2.2ml), and to the mixture was added, under ice-cooling, triacetoxysodium borohydride (4.7g). Under nitrogen atmosphere, the mixture was stirred
10 at room temperature for 5 hours, and to the mixture were added, under ice-cooling, 37% formalin (1.8ml) and triacetoxysodium borohydride (5g). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. The residue was
15 neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel
20 column (ethyl acetate/hexane) to give N-(1,3-dimethoxypropan-2-yl)-N-methyl-4-nitrobenzylamine (3.2g) as yellow oil.

1H -NMR (δ ppm, $CDCl_3$) 2.32 (3H, s), 2.97-3.09 (1H, m), 3.36 (6H, s) 3.44-3.63 (4H, m), 3.85 (2H, s), 7.53 (2H, d, $J=9.0$ Hz),
25 8.17 (2H, d, $J=9.0$ Hz).

IR (neat) ν : 2880, 1520, 1346 cm^{-1} .

Reference Example 282

In acetic acid (100ml) was dissolved N-(1,3-dimethoxypropan-2-yl)-N-methyl-4-nitrobenzylamine (3.1g), and to
30 the mixture was added reduced iron (3.2g) little by little. The mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added ethyl acetate, and precipitates were filtered off. The filtrate was washed with sodium hydroxide solution, water and
35 saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the

residue dissolved in ethyl acetate. To the mixture was added 4N hydrochloric acid-ethyl acetate, and precipitates were filtered and washed with diethylether. The mixture was dissolved in water, and the mixture was neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-((N-(1,3-dimethoxypropan-2-yl)-N-methylamino)methyl)-aniline (2.4g) as red oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.29 (3H, s), 2.95-3.07 (1H, m), 3.34 (6H, s), 3.42-3.58 (4H, m), 3.61 (2H, s), 6.64 (2H, d, $J=8.4\text{Hz}$), 7.11 (2H, d, $J=8.4\text{Hz}$).

IR(neat) ν : 3357, 2880, 1615, 1518 cm^{-1} .

Reference Example 283

In 1,2-dichloroethane (50ml) were dissolved p-nitro-benzaldehyde (5g) and 2-methoxyethylamine (2.7g), and to the mixture was added, under ice-cooling, triacetoxysodium borohydride (9.8g). Under nitrogen atmosphere, the mixture was stirred at room temperature for 4 hours, and to the mixture were added, under ice-cooling, 37% formalin (3.8ml) and triacetoxysodium borohydride (10g). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and the solvent was evaporated. The residue was neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give N-(2-methoxyethyl)-N-methyl-4-nitrobenzylamine (5.9g) as yellow oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.28 (3H, s), 2.63 (2H, t, $J=5.6\text{Hz}$), 3.35 (3H, s), 3.52 (2H, t, $J=5.6\text{Hz}$), 3.65 (2H, s), 7.52 (2H, d, $J=8.8\text{Hz}$), 8.18 (2H, d, $J=8.8\text{Hz}$).

IR(neat) ν : 2814, 1605, 1520, 1346 cm^{-1} .

Reference Example 284

In acetic acid (100ml) was dissolved N-(2-methoxyethyl)-N-methyl-4-nitrobenzylamine (5.9g), and to the mixture was added reduced iron (7.5g) little by little. The mixture was stirred at room temperature overnight, and the solvent was evaporated. To the residue was added ethyl acetate, and precipitates were filtered off. The filtrate was washed with sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 4-((N-(2-methoxyethyl)-N-methylamino)methyl)aniline (3.4g) as red oil.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 2.24 (3H, s), 2.57 (2H, t, $J=6.0\text{Hz}$), 3.33 (3H, s), 3.44 (2H, s), 3.50 (2H, t, $J=6.0\text{Hz}$), 6.64 (2H, d, $J=8.4\text{Hz}$), 7.09 (2H, d, $J=8.4\text{Hz}$).

IR(neat) ν : 3349, 2813, 1615, 1518 cm^{-1} .

Reference Example 285

In THF (350ml) was dissolved 5-bromoanthranilic acid (40.06g), and the mixture was cooled to 0°C . To the mixture was added dropwise a solution of 10.0M borane dimethylsulfide in THF (54.5ml), and the mixture was stirred at room temperature for 4.5 hours. The mixture was cooled to 0°C , and to the mixture was added dropwise 3N sodium hydroxide solution. The mixture was stirred at room temperature overnight, and to the mixture was added granulated sodium hydroxide to adjust the mixture to pH 11. The aqueous layer was saturated with potassium carbonate, and the THF layer was separated. The aqueous layer was extracted with ether (100ml \times 5). The organic layers were combined and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give (2-amino-5-bromophenyl)methanol (36.66g, 100%).

$^1\text{H NMR}$ (200MHz, CDCl_3) δ 4.62 (2H, s), 7.20 (1H, s), 7.23-7.26 (1H, m).

35 Reference Example 286

To acetone (300ml) were added (2-amino-5-

bromophenyl)methanol (23.32g) and active manganese dioxide (58.5g), and the mixture was stirred at room temperature for 17.5 hours and filtered. The solvent was evaporated under reduced pressure to give 2-amino-5-bromobenzaldehyde (16.41g, 71%).

¹H NMR (200MHz, CDCl₃) δ 6.10-6.20 (2H, br), 6.57 (1H, d, J=8.8Hz), 7.38 (1H, dd, J=8.8, 2.4Hz), 7.59 (1H, d, J=2.4Hz), 9.81 (1H, s).

Reference Example 287

To acetic acid anhydride (34.8ml) was added formic acid (17.0ml) at 0°C, and the mixture was stirred at 60°C for 2 hours, cooled and diluted with THF (200ml). In THF (100ml) was dissolved 2-amino-5-bromobenzaldehyde (16.40g), and the mixture was added dropwise to the previously prepared solution of formic acid anhydride in THF at 0°C. The mixture was stirred at 0°C for 2 hours, and the solvent was evaporated under reduced pressure. The residue was washed with hexane and filtered to give 4-bromo-2-formylphenylformamide (15.24g, 82%).

¹H NMR (200MHz, CDCl₃) δ 7.72 (1H, dd, J=8.8, 2.6Hz), 7.83 (1H, d, J=2.6Hz), 8.53 (1H, s), 8.68 (1H, d, J=9.2Hz), 9.88 (1H, s), 10.94 (1H, br).

Reference Example 288

To 4-bromo-2-formylphenylformamide (18.07g), ethyl 4-bromobutyrate (30.9g) and potassium carbonate (21.9g) was added DMF (160ml), and the mixture was stirred at 70°C for 24 hours. The mixture was dilute with ethyl acetate (1400ml), washed with water (300ml \times 3) and saturated brine (150ml), and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (300g, hexane:ethyl acetate=4:1 \rightarrow 1:1) to give ethyl 4-(4-bromo-2,N-diformylanilino)butyrate (21.56g, 80%).

¹H NMR (200MHz, CDCl₃) (syn:anti=5:2 or 2:5) δ 1.23 (2.1H, t, J=7.2Hz), 1.25 (0.9H, t, J=7.2Hz), 1.87 (2H, quint, J=7.5Hz), 2.35 (1.4H, t, J=7.3Hz), 2.36 (0.6H, t, J=6.8Hz),

3.78 (0.6H, t, J=7.5Hz), 3.85 (1.4H, t, J=7.6Hz), 4.10 (1.4H, q, J=6.9Hz), 4.15 (0.6H, q, J=7.2Hz), 7.17 (0.3H, d, J=8.4Hz), 7.24 (0.7H, d, J=8.6Hz), 7.81 (0.3H, dd, J=8.4, 2.4Hz), 7.82 (0.7H, dd, J=8.4, 2.4Hz), 8.09 (0.3H, d, J=2.4Hz), 8.10 (0.7H, d, J=2.4Hz), 8.19 (0.7H, s), 8.39 (0.3H, s), 9.92 (0.3H, s), 10.04 (0.7H, s).

Reference Example 289

In t-butanol (500ml) were dissolved ethyl 4-(4-bromo-2,N-diformylanilino)butyrate (15.32g) and potassium t-butoxide (5.53g), and the mixture was refluxed for 30 minutes. To the mixture were added water (500ml) and 1N hydrochloric acid (50ml), and the mixture was extracted with ethyl acetate (1000ml). The organic layer was washed with saturated brine (200ml) and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (300g, hexane:ethyl acetate=4:1→1:1) to give ethyl 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylate (3.13g, 22%) and 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (1.39g, 10%).

Ethyl 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylate;

mp 150.5-152°C.

¹H NMR (200MHz, CDCl₃) δ 1.34 (3H, t, J=7.1Hz), 2.93 (2H, t, J=4.9Hz), 3.80 (2H, t, J=5.7Hz), 4.28 (2H, q, J=7.2Hz), 7.00 (1H, d, J=8.4Hz), 7.50 (1H, dd, J=8.4, 2.2Hz), 7.57 (1H, s), 7.66 (1H, d, J=2.2Hz), 8.46 (1H, s).

IR (KBr) 1707, 1678, 1491, 1358, 1265, 1235, 1194, 1088 cm⁻¹.

Anal. Calcd. for C₁₄H₁₁NO₃Br: C, 51.87; H, 4.35; N, 4.32.

Found: C, 51.81; H, 4.35; N, 4.19.

7-Bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylic acid;

mp 248-249.5°C.

¹H NMR (200MHz, DMSO-d₆) δ 2.73 (2H, td, J=5.1, 1.2Hz), 3.67 (2H, t, J=5.9Hz), 7.33 (1H, d, J=8.4Hz), 7.57 (1H, s), 7.61 (1H, dd, J=8.4, 2.6Hz), 7.91 (1H, d, J=2.4Hz), 8.48 (1H,

s).

IR (KBr) 1665, 1491, 1431, 1360, 1300, 1281, 1252, 1196, 999, 918, 841, 754 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{NO}_3\text{Br}$: C, 48.67; H, 3.41; N, 4.73.

5 Found: C, 48.70; H, 3.56; N, 4.54.

Reference Example 290

In 1N sodium hydroxide (13.0ml) and THF:ethanol (1:1, 50ml) was dissolved ethyl 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylate (2.77g), and the mixture was stirred at room temperature for 15 hours. To the mixture was added 1N hydrochloric acid (12.5ml), and the mixture was concentrated. To the residue was added water (200ml), and the mixture was adjusted to pH 2 with 1N hydrochloric acid. The mixture was extracted with ethyl acetate (300ml $\times 3$), and the organic layer was dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (2.52g, 100%).

Reference Example 291

20 To a solution of 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (3.28g) in DMF (30ml) was added dropwise thionyl chloride (2.0ml) at 0°C , and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, thionyl chloride and DMF were evaporated, and the residue was dissolved in dichloromethane (40ml). To a solution of 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline (3.90g) and triethylamine (11.6ml) in dichloromethane (40ml) was added dropwise the previously prepared chloride solution at 0°C , and the mixture was stirred at room temperature for 7 hours. The mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate (400ml), washed with water (100ml $\times 2$) and saturated brine (50ml), and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (200g, ethyl acetate \rightarrow ethyl

acetate/ethanol=10:1) to give 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]-phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (2.13g, 39%).

5 mp 173-175°C.

¹H NMR (200MHz, CDCl₃) δ 1.66-1.77 (4H, m), 2.21 (3H, s), 2.58-2.73 (1H, m), 3.02 (2H, t, J=4.8Hz), 3.37 (2H, td, J=10.3, 2.9Hz), 3.58 (2H, s), 3.87 (2H, t, J=5.5Hz), 4.02-4.08 (2H, m), 7.03 (1H, d, J=8.4Hz), 7.32 (2H, d, J=8.4Hz), 1H was concealed under 7.27-7.34, 7.50 (1H, s), 7.51 (1H, dd, J=8.5, 2.3Hz), 7.52 (2H, d, J=8.4Hz), 7.65 (1H, d, J=2.2Hz), 8.49 (1H, s).
10 IR (KBr) 2953, 2845, 1669, 1599, 1520, 1358, 1316, 1260, 1192, 733 cm⁻¹.

15 Anal. Calcd. for C₂₅H₂₈N₃O₃Br: C, 60.24; H, 5.66; N, 8.43.
Found: C, 60.15; H, 5.69; N, 8.49.

Reference Example 292

To t-butyl 7-bromo-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylate (4.0g), 4-ethoxyphenyl borate
20 (2.35g), 1M potassium carbonate solution (25ml) and ethanol (25ml) was added toluene (100ml), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphine palladium (0.55g), and the mixture was refluxed under argon
25 atmosphere overnight. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column (ethyl acetate/hexane) to give t-butyl 7-(4-ethoxyphenyl)-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylate (4.0g) as yellow crystals.
30 mp 140-142°C.

¹H-NMR(δ ppm, CDCl₃) 1.43 (3H, t, J=7.0Hz), 1.54 (9H, s), 2.82 (2H, t, J=4.8Hz), 3.05 (3H, s), 3.27 (2H, t, J=4.8Hz), 4.07
35 (2H, q, J=7.0Hz), 6.83 (1H, d, J=8.4Hz), 6.95 (2H, d, J=8.8Hz), 7.38-7.49 (4H, m), 7.66 (1H, s).

IR(KBr) ν : 2978, 1694 cm^{-1} .

Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{NO}_3$:

C, 75.96; H, 7.70; N, 3.69.

Found C, 75.91; H, 7.89; N, 3.49.

5 Reference Example 293

In dimethoxyethane (100ml) was dissolved t-butyl 7-(4-ethoxyphenyl)-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylate (4.0g), and to the mixture was added 6N hydrochloric acid (25ml). The mixture was refluxed for 3
10 hours, and the solvent was evaporated. Precipitated yellow powder was filtered and washed with ethyl acetate-hexane to give 7-(4-ethoxyphenyl)-1-methyl-2,3-dihydro-1-benzazepine-4-carboxylic acid hydrochloride (3.8g).
mp 245-254 $^{\circ}\text{C}$ (dec.).

15 ^1H -NMR(δ ppm, $\text{DMSO}-d_6$) 1.35 (3H, t, $J=7.0\text{Hz}$), 2.77 (2H, br), 3.02 (3H, s), 3.25 (2H, br), 4.05 (2H, q, $J=7.0\text{Hz}$), 6.94-6.98 (3H, m), 7.49-7.68 (5H, m).

IR(KBr) ν : 2976, 2880, 2475, 1701 cm^{-1} .

Reference Example 294

20 In 1N hydrochloric acid (25ml) and ethanol (20ml) was dissolved ethyl 7-bromo-1-formyl-2,3-dihydro-1-benzazepine-4-carboxylate (1165mg), and the mixture was refluxed for 2 hours. The mixture was neutralized with saturated sodium hydrogen carbonate solution, and the
25 mixture was extracted with ethyl acetate (300ml). The organic layer was washed with water (100ml) and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (150g, hexane/ethyl
30 acetate=9:1) to give ethyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (628mg, 59%).

mp 120-121 $^{\circ}\text{C}$.

^1H NMR (200MHz, CDCl_3) δ 1.34 (3H, t, $J=7.1\text{Hz}$), 2.86 (2H, td, $J=4.8, 1.2\text{Hz}$), 3.36 (2H, t, $J=4.8\text{Hz}$), 4.25 (2H, q, $J=7.1\text{Hz}$), 4.51-4.66 (1H, br), 6.49 (1H, d, $J=8.8\text{Hz}$), 7.15
35 (1H, dd, $J=8.7, 2.3\text{Hz}$), 7.39 (1H, d, $J=2.2\text{Hz}$), 7.53 (1H,

s).

IR (KBr) 3377, 2978, 1694, 1493, 1248, 1209, 1173, 1090, 812 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{BrNO}_2$: C, 52.72; H, 4.76; N, 4.73.

5 Found: C, 52.54; H, 4.88; N, 4.60.

Reference Example 295

In dichloromethane (30ml) were dissolved 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylic acid ethyl (457mg) and triethylamine (1.29ml), and to the mixture was added dropwise at 0°C trifluoromethanesulfonic acid anhydride (1.56ml). The mixture was stirred at 0°C for 4 hours, and to the mixture was added water (50ml) at 0°C . The mixture was extracted with dichloromethane (100ml), and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50g, hexane/ethyl acetate=9:1) to give ethyl 7-bromo-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-4-carboxylate (516mg, 78%).

20 ^1H NMR (200MHz, CDCl_3) δ 1.36 (3H, t, $J=7.5\text{Hz}$), 3.00 (2H, t, $J=6.0\text{Hz}$), 3.91-4.03 (2H, m), 4.30 (2H, q, $J=7.2\text{Hz}$), 7.38 (1H, d, $J=8.4\text{Hz}$), 7.45 (1H, dd, $J=8.8, 2.2\text{Hz}$), 7.63 (1H+1H, s).

IR (KBr) 2982, 1713, 1487, 1397, 1252, 1227, 1194, 1142, 1100, 1090, 700, 627 cm^{-1} .

Reference Example 296

In water/ethanol/toluene (1:1:10, 36.0ml) 4-methylphenyl borate (194mg) and ethyl 7-bromo-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-4-carboxylate (510mg) were dissolved, and to the mixture was added potassium carbonate (395mg). The mixture was stirred under argon atmosphere for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine) palladium (138mg). Under argon atmosphere, the mixture was refluxed for 17 hours, and the mixture was diluted with ethyl acetate (150ml) and washed with water (50ml) and saturated brine

(50ml). The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50g, hexane/ethyl acetate=9:1) to give ethyl 7-(4-methylphenyl)-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-4-carboxylate (469mg, 90%).

¹H NMR (200MHz, CDCl₃) δ 1.37 (3H, t, J=7.2Hz), 2.41 (3H, s), 3.02 (2H, t, J=6.0Hz), 3.99-4.05 (2H, m), 4.31 (2H, q, J=7.1Hz), 7.27 (2H, d, J=8.0Hz), 7.43-7.56 (4H, m), 7.60-7.68 (1H, m), 7.77 (1H, s).

IR (KBr) 2982, 1709, 1495, 1395, 1246, 1225, 1192, 1152, 1096, 812, 642, 588 cm⁻¹.

Reference Example 297

In 1N sodium hydroxide solution (3.0ml) and THF/ethanol (1:1, 12.0ml) was dissolved 7-(4-methylphenyl)-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid ethyl (463mg), and the mixture was stirred at room temperature for 14 hours. The mixture was neutralized with 1N hydrochloric acid (3.5ml) and concentrated. To the residue was added water (40ml), and the mixture was extracted with ethyl acetate (100ml×3). The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 7-(4-methylphenyl)-1-[(trifluoromethyl)sulfonyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (393mg, 91%).

¹H NMR (200MHz, DMSO-d₆) δ 2.39 (3H, s), 2.94 (2H, t, J=6.2Hz), 4.00-4.08 (2H, m), 7.28 (2H, d, J=8.6Hz), 7.41-7.49 (1H, m), 7.56 (2H, d, J=8.4Hz), 7.61-7.66 (1H, m), 7.73-7.77 (1H, m), 8.00 (1H, s).

Reference Example 298

To a solution of 4-nitrobenzaldehyde (3.02g) and 2-aminopyridine (1.88g) in 1,2-dichloroethane (70ml) were added triacetoxy sodium borohydride (5.93g) and acetic acid (1.14ml), and the mixture was stirred under nitrogen atmosphere at room temperature for 2 hours and concentrated.

To the residue was added sodium bicarbonate solution, and the mixture was extracted with ethyl acetate, washed with brine, dried (anhydrous magnesium sulfate) and concentrated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane =1/1), and to the purified materials were added ethyl acetate/diethylether and 1N hydrochloric acid. The aqueous layer was extracted and washed with diethylether, and to the mixture was added sodium carbonate. The mixture was extracted with ethyl acetate, and the extract was dried (anhydrous magnesium sulfate), concentrated and recrystallized from ethyl acetate/hexane to give 2-[(4-nitrophenyl)methylamino]pyridine (1.63g) as pale yellow crystals.

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15
¹H-NMR (200MHz, CDCl₃) δ : 4.67 (2H, d, J = 6.0), 4.9-5.1 (1H, brm), 6.37 (1H, d, J = 8.4), 6.63 (1H, dd, J = 5.1, 6.9), 7.35-7.45 (1H, m), 7.52 (2H, d, J = 8.8), 8.15-8.25 (1H, m), 8.18 (2H, d, J = 8.8).

IR (KBr) 1601, 1516, 1460, 1348, 1281, 1159, 999, 772cm⁻¹

20 Anal for C₁₂H₁₁N₃O₂

Calcd. C, 62.87; H, 4.84; N, 18.33:

Found. C, 62.69; H, 4.69; N, 18.20.

Reference Example 299

25 To a solution of nickel bromide (44mg) in methanol (4ml)/THF (4ml) was added sodium boro hydride (40mg), and the mixture was stirred. To the mixture was added 2-[(4-nitrophenyl)methylamino]pyridine (0.92g) and then sodium boro hydride (414mg), and the mixture was stirred at room temperature for 1 hour. To the mixture was added
30 nickel bromide (44mg) and sodium boro hydride (454mg), and the mixture was stirred at room temperature for 2 hours. Insoluble materials were filtered off with sellaita, and to the filtrate was added sodium bicarbonate solution. The mixture was extracted with ethyl acetate and washed with
35 brine. The extract was dried (anhydrous magnesium sulfate) and concentrated, and the residue was purified twice with

silica gel column chromatography (ethyl acetate/hexane =1/1) to give 2-[(4-aminophenyl)methylamino]pyridine (369mg) as pale red solid.

¹H-NMR (200MHz, CDCl₃) δ : 3.4-3.8 (2H, br), 4.36 (2H, d, J = 5.2), 4.7-4.85 (1H, br), 6.37 (1H, d, J = 8.4), 6.58 (1H, dd, J = 5.2, 8.0), 6.66 (2H, d, J = 8.4), 7.15 (2H, d, J = 8.4), 7.35-7.45 (1H, m), 8.05-8.15 (1H, m).

IR (KBr) 1603, 1578, 1514, 1443, 1335, 1294, 1159, 818, 770cm⁻¹

10

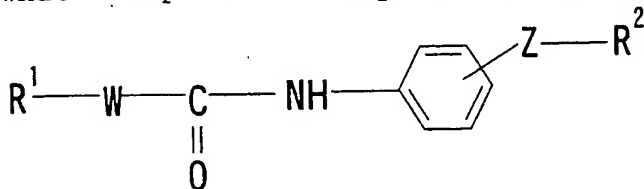
Industrial Applicability

The compound of the formula (I') or a salt thereof of the present invention has potent CCR5 antagonistic activity and can be advantageously used for the treatment or prophylaxis of infectious disease of various HIV in human (e.g. AIDS).

15

CLAIMS

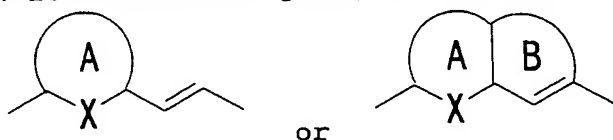
1. A pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



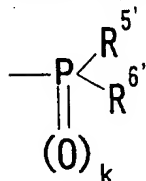
5

wherein R^1 is an optionally substituted 5- to 6-membered ring;

W is a divalent group of the formula:



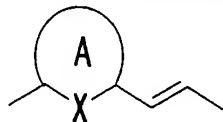
- 10 wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or
- 15 a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a
- 20 nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an
- 25 optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic

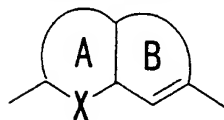
group together with the adjacent phosphorus atom, or a salt thereof.

2. A composition according to claim 1, wherein R¹ is benzene, furan, thiophene, pyridine, cyclopentane,
- 5 cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted.
3. A composition according to claim 1, wherein R¹ is an optionally substituted benzene.
- 10 4. A composition according to claim 1, wherein the ring A is furan, thiophene, pyrrole, pyridine or benzene, each of which may be substituted.
5. A composition according to claim 1, wherein the ring A is an optionally substituted benzene.
- 15 6. A composition according to claim 1, wherein W is a group of the formula:



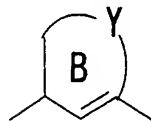
wherein each symbol is as defined in claim 1.

7. A composition according to claim 1, wherein W is a group
- 20 of the formula:



wherein each symbol is as defined in claim 1.

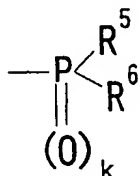
8. A composition according to claim 7, wherein the ring B is a 5- to 7-membered ring group of the formula:



- 25 wherein Y is -Y'-(CH₂)_m- (Y' is -S-, -O-, -NH- or -CH₂-, and m is an integer of 0-2), -CH=CH- or -N=CH-), which may have a substituent at any possible position.

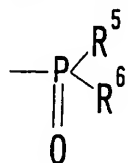
9. A composition according to claim 8, wherein Y is -
- 30 Y'-(CH₂)_m- (Y' is -S-, -O-, -NH- or -CH₂-).

10. A composition according to claim 8, wherein Y is -
 $(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-$ or $-\text{O}-(\text{CH}_2)_2-$.
11. A composition according to claim 10, wherein the ring
 A is an optionally substituted benzene.
- 5 12. A composition according to claim 1, wherein Z is an
 optionally substituted C_{1-3} alkylene.
13. A composition according to claim 1, wherein Z is a
 divalent group of the formula: $-\text{Z}'-(\text{CH}_2)_n-$ (Z' is $-\text{CH}(\text{OH})-$,
 $-\text{C}(\text{O})-$ or $-\text{CH}_2-$, and n is an integer of 0-2) in which an
 10 optional methylene group may be substituted.
14. A composition according to claim 1, wherein Z is
 methylene.
15. A composition according to claim 1, wherein Z is
 substituted at para position of the benzene ring.
- 15 16. A composition according to claim 1, wherein R^2 is (1)
 an optionally substituted amino group wherein a nitrogen
 atom may form a quaternary ammonium, (2) an optionally
 substituted nitrogen-containing heterocyclic ring group
 which may contain a sulfur atom or an oxygen atom as ring
 20 constituting atoms and wherein a nitrogen atom may form a
 quaternary ammonium, (3) a group binding through a sulfur
 atom or (4) a group of the formula:

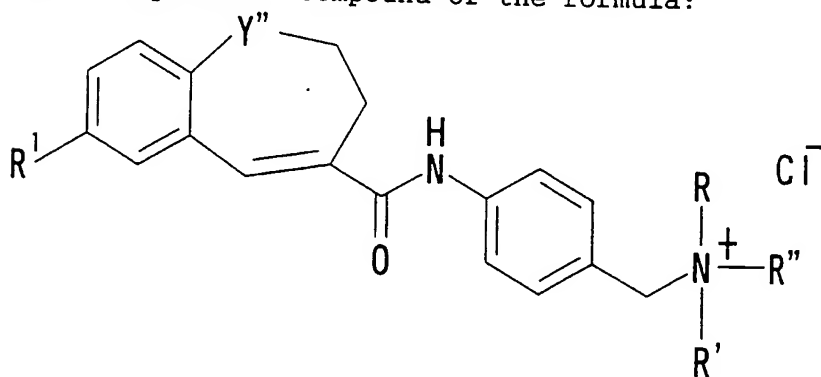


- wherein k is 0 or 1, and when k is 0, a phosphorus atom may
 25 form a phosphonium; and R^5 and R^6 are independently an
 optionally substituted hydrocarbon group or an optionally
 substituted amino group, and R^5 and R^6 may bind to each other
 to form a cyclic group together with the adjacent phosphorus
 atom.
- 30 17. A composition according to claim 1, wherein R^2 is (1)
 an optionally substituted amino group wherein a nitrogen
 atom may form a quaternary ammonium, (2) an optionally
 substituted nitrogen-containing heterocyclic ring group

which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium or (3) a group of the formula:



- 5 wherein R⁵ and R⁶ are independently an optionally substituted hydrocarbon group, and R⁵ and R⁶ may bind to each other to form a cyclic group together with the adjacent phosphorus atom.
18. A composition according to claim 1, wherein R² is an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium.
19. A composition according to claim 1, wherein R² is a group of the formula: -N⁺RR'R"
- wherein R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group.
20. A pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



- 20 wherein R¹ is an optionally substituted benzene or an optionally substituted thiophene; Y'' is -CH₂-, -S- or -O-; and R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group.
21. A composition according to claim 20, wherein R and R'

are independently an optionally substituted acyclic hydrocarbon group.

22. A composition according to claim 20, wherein R and R' are independently an optionally substituted C₁₋₆ alkyl group.

5 23. A composition according to claim 20, wherein R" is an optionally substituted alicyclic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group.

10 24. A composition according to claim 20, wherein R" is an optionally substituted C₃₋₈ cycloalkyl group.

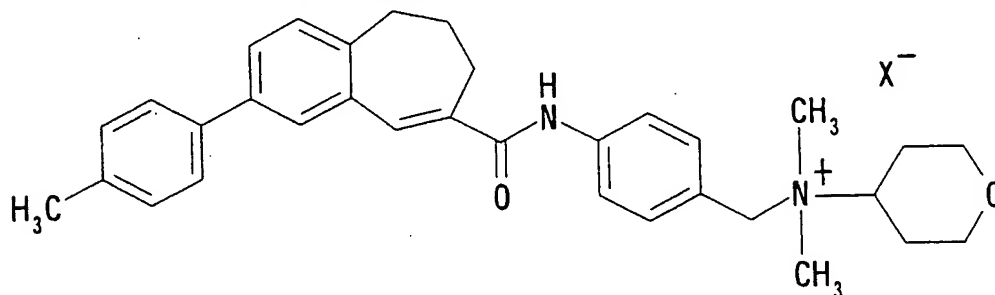
25. A composition according to claim 20, wherein R" is an optionally substituted cyclohexyl.

15 26. A composition according to claim 20, wherein R" is an optionally substituted saturated alicyclic heterocyclic ring group.

27. A composition according to claim 20, wherein R" is an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl.

20 28. A composition according to claim 20, wherein R" is an optionally substituted tetrahydropyranyl.

29. A pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



25 wherein X⁻ is an anion.

30. A composition according to claim 29, wherein X is a halogen atom.

31. A pharmaceutical composition for antagonizing CCR5 which comprises

30 N-methyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-

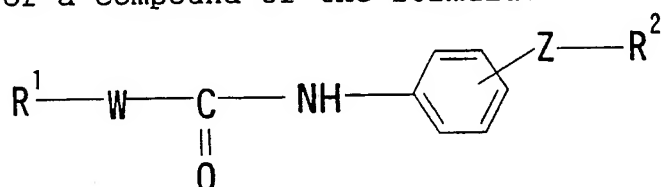
- benzocyclohepten-8-yl]carbonyl]amino]benzyl]-
piperidinium iodide,
N-methyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-
benzoxepin-4-yl]carbonyl]amino]benzyl]piperidinium
5 iodide,
N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-
phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-
carboxmide,
N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-
10 phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1-
benzoxepine-4-carboxmide,
7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-
yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-
carboxmide,
15 N,N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-
benzocyclohepten-8-yl]carbonyl]amino]benzyl]-N-
(tetrahydropyran-4-yl)ammonium iodide,
N,N-dimethyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-
benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(4-
20 oxocyclohexyl)ammonium chloride,
N,N-dimethyl-N-[4-[[[7-(4-ethoxyphenyl)-2,3-dihydro-1-
benzoxepin-4-yl]carbonyl]amino]benzyl]-N-
(tetrahydropyran-4-yl)ammonium chloride,
or a salt thereof.
25 32. A composition according to claim 1, which is for the
treatment or prophylaxis of infectious disease of HIV.
33. A composition according to claim 1, which is for the
treatment or prophylaxis of AIDS.
34. A composition according to claim 1, which is for the
30 prevention of the progression of AIDS.
35. A composition according to claim 32, which is used in
combination with a protease inhibitor and/or a reverse
transcriptase inhibitor.
36. A composition according to claim 35, wherein the
35 reverse transcriptase inhibitor is zidovudine, didanosine,
zalcitabine, lamivudine, stavudine, nevirapine or

delavirdine.

37. A composition according to claim 35, wherein the protease inhibitor is saquinavir, ritonavir, indinavir or nelfinavir.

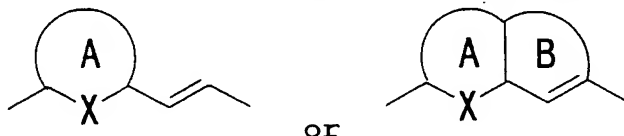
5 38. Use of the compound as claimed in claim 1 or a salt thereof in combination with a protease inhibitor and/or a reverse transcriptase inhibitor for the treatment or prophylaxis of infectious disease of HIV.

10 39. A method for antagonizing CCR5 which comprises administering to a mammal in need thereof an effective amount of a compound of the formula:



wherein R¹ is an optionally substituted 5- to 6-membered ring;

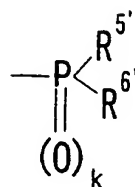
15 W is a divalent group of the formula:



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R² is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:

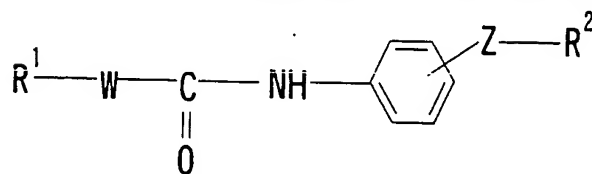
20

25



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^{5'} and R^{6'} are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R^{5'} and R^{6'} may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof.

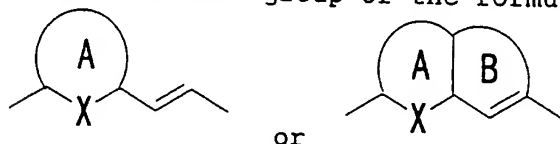
40. Use of a compound of the formula:



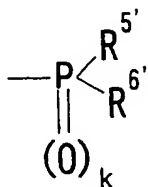
10

wherein R¹ is an optionally substituted 5- to 6-membered ring;

W is a divalent group of the formula:



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R² is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^{5'} and R^{6'} are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R^{5'} and R^{6'} may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof, for the manufacture of a medicament for antagonizing CCR5.

Sequence List

Sequence ID No. 1

Length of Sequence : 34

5 Type of Sequence : nucleic acid

Number of Chain : single

Topology : straight

Kind of Sequence : other nucleic acid synthetic DNA

Sequence:

10 CAGGATCCGA TGGATTATCA AGTGTCAAGT CCAA 34

Sequence ID No. 2

Length of Sequence : 34

Type of Sequence : nucleic acid

15 Number of Chain : single

Topology : straight

Kind of Sequence : other nucleic acid synthetic DNA

Sequence:

TCTAGATCAC AAGCCCACAG ATATTCCTG CTCC 34



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MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM,
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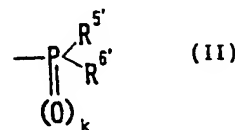
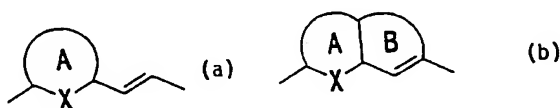
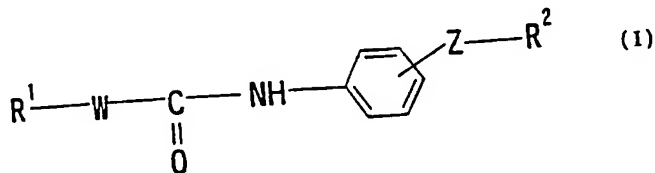
With international search report.

(88) Date of publication of the international search report:
10 September 1999 (10.09.99)

(54) Title: PHARMACEUTICAL COMPOSITION FOR ANTAGONIZING CCR5 COMPRISING ANILIDE DERIVATIVE

(57) Abstract

This invention is to provide a pharmaceutical composition for antagonizing CCR5 which comprises a compound of formula (I) wherein R^1 is an optionally substituted 5- to 6-membered ring; W is a divalent group of formula (a) or (b) wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted C, N or O atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of formula (II) wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^5 and R^6 are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R^5 and R^6 may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof.



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INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/JP 98/05708

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/35 A61K31/445 A61K31/535 A61K31/335 A61K31/665
A61K31/67

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 01267 A (SOHDA TAKASHI ;ODA TSUNEO (JP); TAKEDA CHEMICAL INDUSTRIES LTD (JP) 18 January 1996 cited in the application see abstract see page 33, line 1 - line 9; examples 1-4,10,11 see examples 19-26,56 see claims; examples 69-72 -----	1-5,7,8, 10-17, 32-37

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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G document member of the same patent family

Date of the actual completion of the international search

18 May 1999

Date of mailing of the international search report

25.06.99

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Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

Int. national application No.

PCT/JP 98/05708

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 38-39
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 38-39
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP 98/05708

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are defined by the general formula of claim 1, the search was limited to the inventive part of the molecule and to the compounds mentioned in claims 20-31 (Art. 6 PCT; Guidelines Chapt.II.7 last sentence and Chapt.III,3.7).

Claims searched completely : 20-31

Claims searched

incompletely: 1-19,32-40

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/05708

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601267 A	18-01-1996	AU 2808495 A	25-01-1996
		CA 2191980 A	18-01-1996
		CN 1151744 A	11-06-1997
		EP 0769015 A	23-04-1997
		JP 8073476 A	19-03-1996
		US 5716944 A	10-02-1998

Form PCT/ISA/210 (patent family annex) (July 1992)